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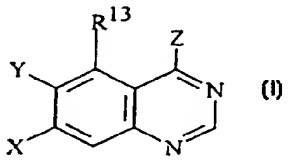

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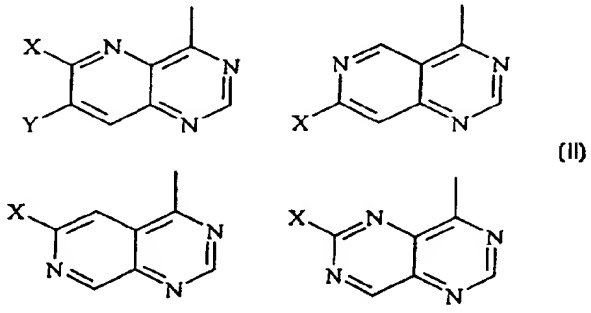

(II)

(57) Abstract

The present invention provides compounds that are irreversible inhibitors of tyrosine kinases of formula (I) or (II). Also provided is a method of treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis and a pharmaceutical composition that comprises a compound that is an irreversible inhibitor of tyrosine kinases. In formulas (I) and (II), Z, X, Y or R^{13} are as defined in the description.

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IRREVERSIBLE BICYCLIC INHIBITORS OF TYROSINE KINASES

FIELD OF THE INVENTION

This invention relates to compounds that are irreversible inhibitors of tyrosine kinases. This invention also relates to a method of treating cancer, atherosclerosis, restenosis, endometriosis, and psoriasis, and to a pharmaceutical composition that comprises a compound that is an irreversible inhibitor of tyrosine kinases.

BACKGROUND OF THE INVENTION

Cancer has been viewed as a disease of the intracellular signalling system, or signal transduction mechanism. Cells receive instructions from many extracellular sources, instructing them to either proliferate or not to proliferate. The purpose of the signal transduction system is to receive these and other signals at the cell surface, get them into the cell, and then pass the signals on to the nucleus, the cytoskeleton, and transport and protein synthesis machinery.

The most common cause of cancer is a series of defects, either in these proteins, when they are mutated, or in the regulation of the quantity of the protein in the cell such that it is over or under produced. Most often, there are key lesions in the cell which lead to a constitutive state whereby the cell nucleus receives a signal to proliferate, when this signal is not actually present. This can occur through a variety of mechanisms. Sometimes the cell may start to produce an authentic growth factor for its own receptors when it should not, the so-called autocrine loop mechanism. Mutations to the cell surface receptors, which usually signal into the cell by means of tyrosine kinases, can lead to activation of the kinase in the absence of ligand, and passing of a signal which is not really there. Alternatively, many surface kinases can be overexpressed on the cell surface leading to an inappropriately strong response to a weak signal. There are many levels inside the cell at which mutation or overexpression can lead to the same

spurious signal arising in the cell, and there are many other kinds of signalling defects involved in cancer. This invention touches upon cancers which are driven by the three mechanisms just described, and which involve cell surface receptors of the epidermal growth factor receptor tyrosine kinase family (EGFR). This family consists of the EGF receptor (also known as Erb-B1), the Erb-B2 receptor, and its constitutively active oncoprotein mutant Neu, the Erb-B3 receptor and the Erb-B4 receptor. Additionally, other biological processes driven through members of the EGF family of receptors can also be treated by compounds of the invention described below.

The EGFR has as its two most important ligands Epidermal Growth Factor (EGF) and Transforming Growth Factor alpha (TGF alpha). The receptors appear to have only minor functions in adult humans, but are apparently implicated in the disease process of a large portion of all cancers, especially colon and breast cancer. The closely related Erb-B2, Erb-B3, and Erb-B4 receptors have a family of Heregulins as their major ligands, and receptor overexpression and mutation have been unequivocally demonstrated as the major risk factor in poor prognosis breast cancer. Additionally, it has been demonstrated that all four of the members of this family of receptors can form heterodimeric signalling complexes with other members of the family, and that this can lead to synergistic transforming capacity if more than one member of the family is overexpressed in a malignancy. Overexpression of more than one family member has been shown to be relatively common in human malignancies.

In addition to cancer, restenosis is also a disease in which undesired cellular proliferation occurs. Restenosis involves the proliferation of vascular smooth muscle cells. Restenosis is a major clinical problem associated with coronary angioplasty and other medical procedures. Restenosis generally occurs within about 0 to 6 months in about 30% to 50% of patients who undergo balloon angioplasty to clear clogged coronary arteries in an effort to treat heart disease due to occluded arteries. The resulting restenosis causes substantial patient morbidity and health care expense.

The process of restenosis is initiated by injury of the blood vessel, including arteries and veins, with the subsequent release of thrombogenic,

vasoactive, and mitogenic factors. Endothelial and deep vessel injury leads to platelet aggregation, thrombus formation, inflammation, and activation of macrophages and smooth muscle cells. These events induce the production of and release of growth factors and cytokines, which in turn may promote their own synthesis and release from target cells. Thus, a self-perpetuating process involving growth factors such as EGF, platelet derived growth factor (PDGF) or fibroblast growth factor (FGFs) is initiated. Thus, it would be useful to have irreversible inhibitors of signal transduction pathways, particularly of tyrosine kinases like EGF, PDGF, FGF, or src tyrosine kinases.

The proliferative skin disease psoriasis has no good cure at present. It is often treated by anticancer agents such as methotrexate, which have very serious side effects, and which are not very effective at the toxicity limited doses which have to be used. It is believed that TGF alpha is the major growth factor overproduced in psoriasis, since 50% of transgenic mice which over express TGF alpha develop psoriasis. This suggests that a good inhibitor of EGFR signalling could be used as antipsoriatic agent, preferably, but not necessarily, by topical dosing.

It is especially advantageous to have irreversible tyrosine kinase inhibitors when compared to reversible inhibitors, because irreversible inhibitors can be used in prolonged suppression of the tyrosine kinase, limited only by the normal rate of receptor resynthesis, also called turnover.

Additional information on the role of src tyrosine kinases in biological processes relating to cancer and restenosis can be found in the following documents, which are all hereby incorporated by reference.

Benjamin C.W. and Jones D.A., Platelet-Derived Growth Factor Stimulates Growth Factor Receptor Binding Protein-2 Association With Src In Vascular Smooth Muscle Cells, *JBC*, 1994;269:30911-30916.

Kovalenko M., et al., Selective Platelet-Derived Growth Factor Receptor Kinase Blockers Reverse Cis-transformation, *Cancer Res*, 1994;54:6106-6114.

Schwartz R.S., et al., The Restenosis Paradigm Revisted: An Alternative Proposal for Cellular Mechanisms, *J Am Coll Cardiol*, 1992;20:1284-1293.

Libby P., et al., Cascade Model for Restenosis - A Special Case of Atherosclerosis Progression, *Circulation*, 1992;86:47-52.

Additional information on the role of EGF tyrosine kinases in biological processes relating to cancer and restenosis can be found in the following document which is hereby incorporated by reference.

Jonathan Blay and Morley D. Hollenberg, Heterologous Regulation Of EGF Receptor Function In Cultured Aortic Smooth Muscle Cells, *Eur J Pharmacol, Mol Pharmacol Sect*, 1989;172(1):1-7.

Information that shows that antibodies to EGF or EGFR show in vivo antitumor activity can be found in the following documents which are hereby incorporated by reference.

Modjtahedi H., Eccles S., Box G., Styles J., Dean C., Immunotherapy Of Human Tumour Xenografts Overexpressing The EGF Receptor With Rat Antibodies That Block Growth Factor-Receptor Interaction, *Br J Cancer*, 1993;67:254-261.

Kurachi H., Morishige K.I., Amemiya K., Adachi H., Hirota K., Miyake A., Tanizawa O., Importance Of Transforming Growth Factor Alpha/Epidermal Growth Factor Receptor Autocrine Growth Mechanism In An Ovarian Cancer Cell Line In Vivo, *Cancer Res*, 1991;51:5956-5959.

Masui H., Moroyama T., Mendelsohn J., Mechanism Of Antitumor Activity In Mice For Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies With Different Isotypes, *Cancer Res*, 1986;46:5592-5598.

Rodeck U., Herlyn M., Herlyn D., Molthoff C., Atkinson B., Varello M., Steplewski Z., Koprowski H., Tumor Growth Modulation By A Monoclonal Antibody To The Epidermal Growth Factor Receptor: Immunologically Mediated And Effector Cell-Independent Effects, *Cancer Res*, 1987;47:3692-3696.

Guan E., Zhou T., Wang J., Huang P., Tang W., Zhao M., Chen Y., Sun Y., Growth Inhibition Of Human Nasopharyngeal Carcinoma In Athymic Mice By Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies, *Internat J Cell Clon*, 1989;7:242-256.

Masui H., Kawamoto T., Sato J.D., Wolf B., Sato G., Mendelsohn J., Growth Inhibition Of Human Tumor Cells In Athymic Mice By Anti-Epidermal

Growth Factor Receptor Monoclonal Antibodies, *Cancer Res*, 1984;44:1002-1007.

In addition, the following documents show the antitumor activity of protein tyrosine kinase inhibitors. The documents are hereby incorporated by reference.

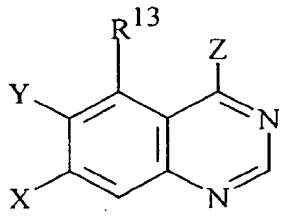
Buchdunger E., Trinks U., Mett H., Regenass U., Muller M., Meyer T., McGlynn E., Pinna L.A., Traxler P., Lydon N.B., 4,5-Dianilinophthalimide: A Protein Tyrosine Kinase Inhibitor With Selectivity For The Epidermal Growth Factor Receptor Signal Transduction Pathway And Potent In Vivo Antitumor Activity, *Proc Natl Acad Sci USA*, 1994;91:2334-2338.

Buchdunger E., Mett H., Trinks U., Regenass U., Muller M., Meyer T., Beilstein P., Wirz B., Schneider P., Traxler P., Lydon N., 4,5-Bis (4-Fluoroanilino)Phthalimide: A Selective Inhibitor Of The Epidermal Growth Factor Receptor Signal Transduction Pathway With Potent In Vivo Mdd Antitumor Activity, *Clinical Cancer Research*, 1995;1:813-821.

Compounds that are reversible inhibitors of tyrosine kinases have been described in US Patent Numbers 5,457,105, 5,475,001, and 5,409,930 and in PCT publication Numbers WO 9519774, WO 9519970, WO 9609294, and WO 9523141. The presently disclosed compounds, which are structurally different from the tyrosine kinase inhibitors described in the above-identified documents, are irreversible inhibitors of tyrosine kinases.

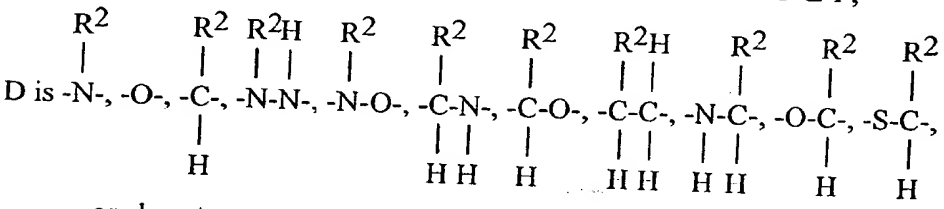
SUMMARY OF THE INVENTION

The present invention provides compounds having the Formula I



I

wherein X is -D-E-F and Y is $-SR^4$, halogen, $-OR^4$, $-NHR^3$, or hydrogen, or X is $-SR^4$, halogen, $-OR^4$, $-NHR^3$, or hydrogen, and Y is -D-E-F;

D is 

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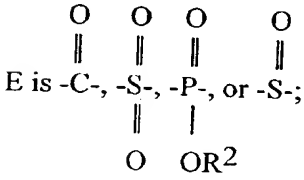
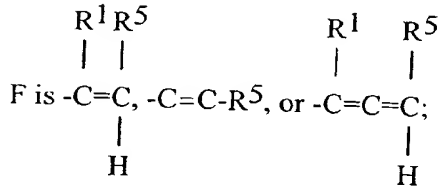
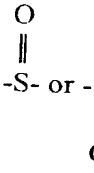
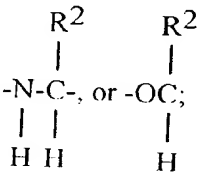
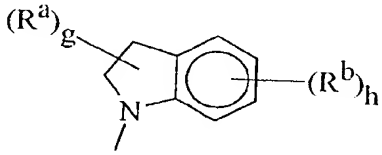
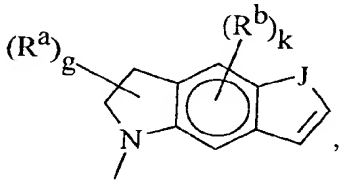
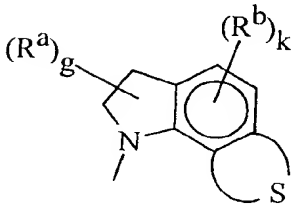
E is 

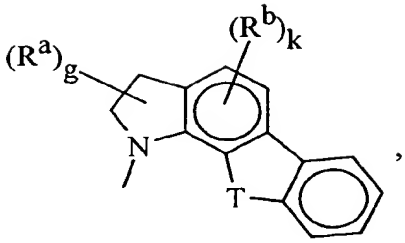
F is 

provided that when E is  D is not 

Z is  ,

 ,

 ,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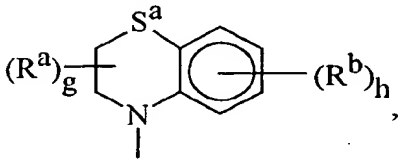
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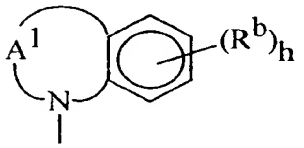

, or —NH— Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N- (C_1-C_4)alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-

substituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is $-Z^aR^{77}$;

J is $-CH_2-$, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is $-CH_2$, -N(H)-, thio, or oxy;

S^a is $-CH_2-$, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylamino, di-[(C_1-C_4)alkyl]amino, and (C_2-C_4)alkanoylamino;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the

substituents are selected from -OH, $-NH_2$, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_nOH$, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl;

Z^1, Z^2, or Z^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NH(C_3$-C_8 cycloalkyl), $-N(C_3$-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl, C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, $-CH_2$-, -S-, SO_2, -NH-, -O-, $-OCH_2$-, $-S-CH_2$-, $-SO_2CH_2$-, or $-CH_2CH_2$-;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C{=}CH_2$, $-CH{=}CH-(C_1$-$C_6)$alkyl, $-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$, $-(CH_2)_nNH(C_1$-C_6alkyl), $-(CH_2)_nN(C_1$-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to

three substituents independently selected from Z^1, Z^2, Z^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group above in R^5 can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above;

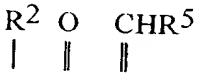
R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^{13} is hydrogen or halogen; and

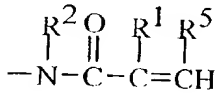
n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

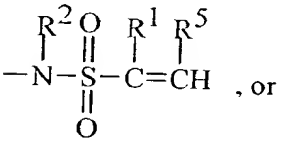
In a preferred embodiment of the compounds of Formula I,

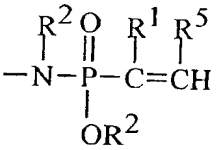
X is  , and Y is hydrogen, or

X is hydrogen, and Y is  .

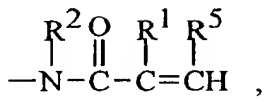
In another preferred embodiment of the compounds of Formula I, Y is -D-E-F, and -D-E-F is

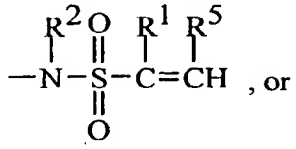
 ,

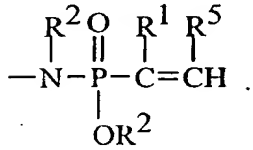
 , or

 .

In another preferred embodiment of the compounds of Formula I, X is -D-E-F, and -D-E-F is







In another preferred embodiment of the compounds of Formula I, R^2 is hydrogen.

In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O$(CH_2)_n$-morpholino.

In another preferred embodiment of the compounds of Formula I, R^5 is carboxy, (C_1-C_6 alkyl)oxycarbonyl or C_1-C_6 alkyl.

In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O$(CH_2)_n$morpholino.

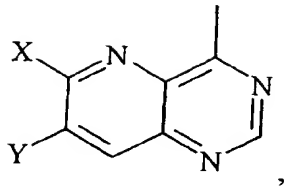
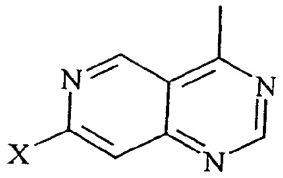
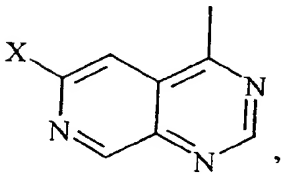
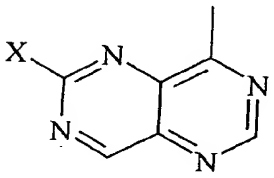
In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O-$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl].

In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O-$(CH_2)_n$-imidazoyl.

In another embodiment, the present invention provides compounds having the Formula II

Q-Z II

wherein Q is




, or

;

p is 0 or 1;

X is -D-E-F and Y is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;

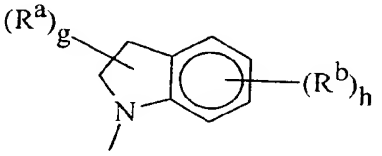
D is -N-, -O-, -C(H)-, -N-N-, -N-O-, -C(H,H)-N-, -C-O-, -C(H,H)-C(H,H)-, -N-C(H,H)-, -O-C(H)-, -S-C(H)-,

or absent;

E is -C(=O)-, -S(=O)-, -P(=O)(OR2)-, or -S(=O)(=O)-;

F is -C(H)=C-, -C=C-R5, or -C(H)=C=C(H)-;

provided that when E is -S(=O)(=O)- or -S(=O)-, D is not -N(H)-C(H,H)-, or -OC(H)-;

Z is 
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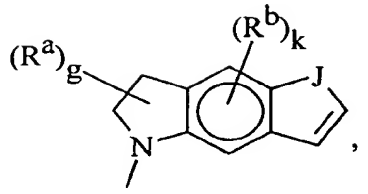

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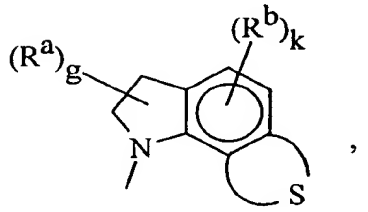

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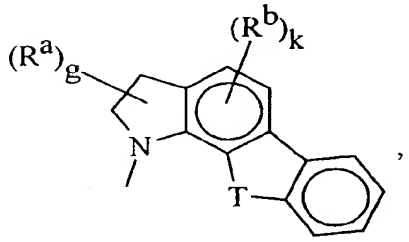

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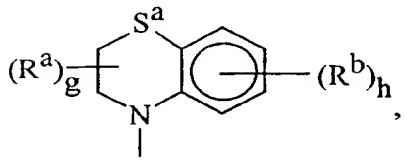

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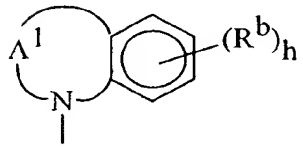


, or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4)alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is -$Z^a R^{77}$;

J is -CH_2-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is -CH_2, -N(H)-, thio, or oxy;

S^a is -CH_2-, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl,

(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylamino, di-[(C_1-C_4)alkyl]amino, and (C_2-C_4)alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl;

E^1, E^2, or E^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NH(C_3-C_8 cycloalkyl), -N(C_3-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl, C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, -CH_2-, -S-, SO_2, -NH-, -O-, -OCH_2-, -S-CH_2-, -SO_2-, or -CH_2CH_2-;

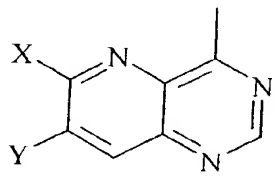
R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -(CH_2)n-N-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -C=CH_2, -CH=CH-(C_1-C_6)alkyl,

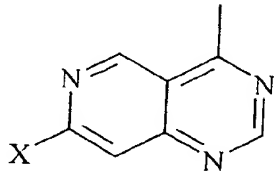
-$(CH_2)_n$-N-hexahydroazepine, -$(CH_2)_nNH_2$,-$(CH_2)_nNH(C_1$-C_6alkyl), -$(CH_2)_nN(C_1$-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E^1, E^2, E^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group can be substituted with -OH, -NH_2 or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

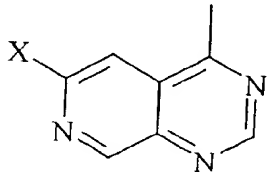
In another preferred embodiment of the compounds of Formula II, Q is



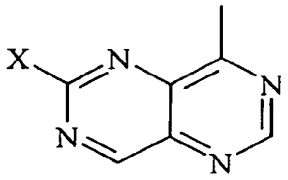
In another preferred embodiment of the compounds of Formula II, Q is



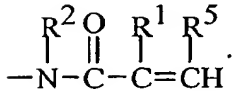
In another preferred embodiment of the compounds of Formula II, Q is



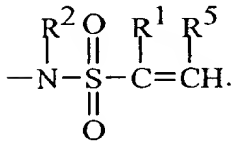
In another preferred embodiment of the compounds of Formula II, Q is



In another preferred embodiment of the compounds of Formula II, X is



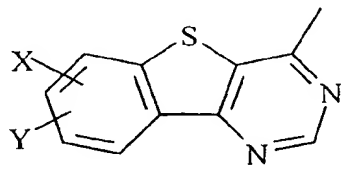
In another preferred embodiment of the compounds of Formula II, X is



In another embodiment, the present invention provides compounds having the Formula II

Q-Z II

wherein Q is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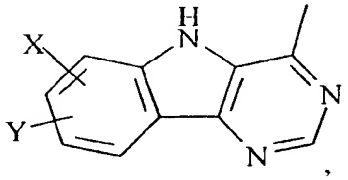
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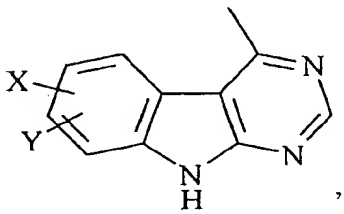
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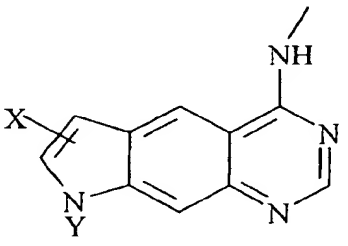
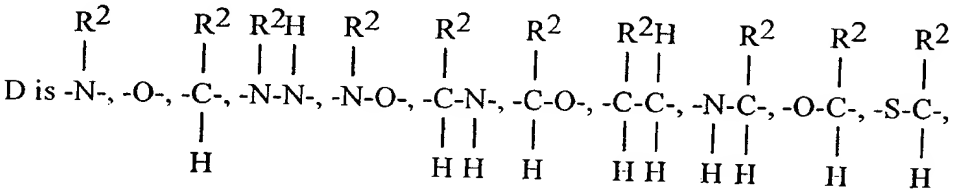
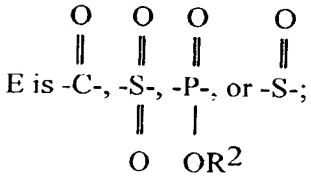

;

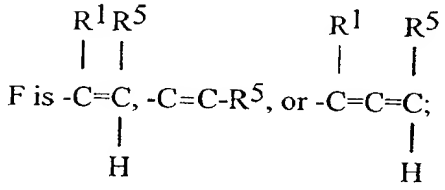
p is 0 or 1;

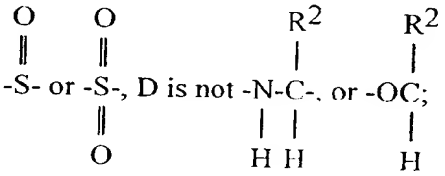
X is -D-E-F, and Y is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;

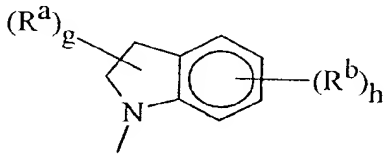
D is 

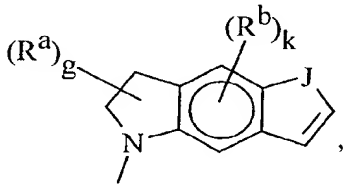
or absent;

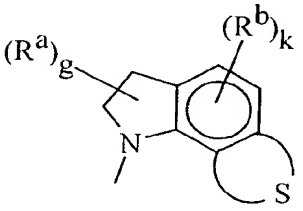
E is 

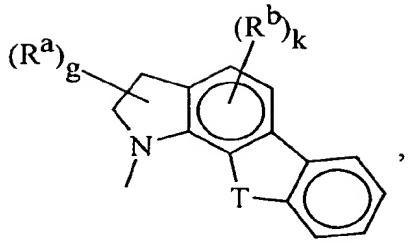
F is 

provided that when E is -S- or -S-, D is not 

Z is 



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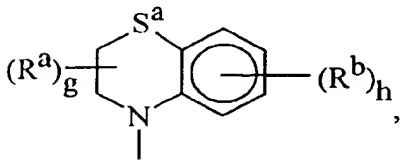
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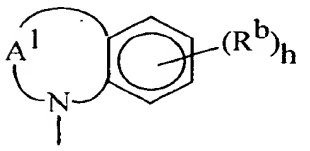

, or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4)alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-

substituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is -Z^aR^{77};

J is -CH_2-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is -CH_2, -N(H)-, thio, or oxy;

S^a is -CH_2-, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylamino, di-[(C_1-C_4)alkyl]amino, and (C_2-C_4)alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the

substituents are selected from -OH, $-NH_2$, or $-N(A)-B$, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_nOH$, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl;

E^1, E^2, or E^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NH(C_3$-C_8 cycloalkyl), $-N(C_3$-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl, C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, $-CH_2$-, -S-, SO_2, -NH-, -O-, $-OCH_2$-, $-S-CH_2$-, $-SO_2$-, or $-CH_2CH_2$-;

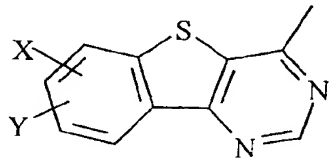
R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C(=CH_2)-$, $-CH=CH-(C_1$-$C_6)$alkyl, $-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$, $-(CH_2)_nNH(C_1$-C_6alkyl), $-(CH_2)_nN(C_1$-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy,

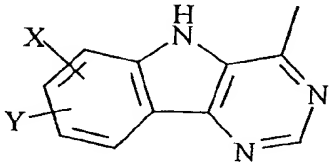
$(C_1\text{-}C_6)$alkyloxycarbonyl, N-$(C_1\text{-}C_6)$alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E^1, E^2, E^3 or a monocyclic heteroaryl group, and each $C_1\text{-}C_6$ alkyl group can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

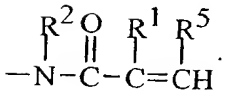
In another preferred embodiment of the compounds of Formula III, Q is



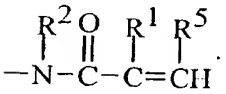
In another preferred embodiment of the compounds of Formula III, Q is



In another preferred embodiment of the compounds of Formula III, X is



In another preferred embodiment of the compounds of Formula III, X is



In another preferred embodiment, Q is a 6-substituted benzothieno[3,2-d]pyrmid-4-yl.

The present invention also provides a pharmaceutically acceptable composition that comprises a compound of Formula I or II.

The present invention also provides a method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Formula I or II.

The present invention also provides a method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis, a therapeutically effective amount of a compound of Formula I or II.

The present invention also provides a method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Formula I or II.

The present invention also provides a method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Formula I or II.

The present invention also provides a method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Formula I or II.

The present invention also provides a method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient in need of tyrosine kinase inhibition a tyrosine kinase inhibiting amount of a compound of Formula I or II.

In a most preferred embodiment the present invention provides the following compounds:

N-[4-(6-Bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylamide;

N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]propynamide;

N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]propynamide;

N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]propynamide;

N-[4-(4-6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] -4,4,4-trifluorobut-2-enamide;

N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacryl-amide;

N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)quinazoline;

6-(S-Vinylsulfonamido)-4-(6-pyrrol-1-yl-2,3-dihydroindol-1-yl)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Pyrrol-1-yl-2,3-dihydroindol-1-yl)-7-[4-(N,N-dimethylamino) butoxy] quinazolin-6-yl]acrylamide

N-[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(Octahydroindol-1-yl)-7-[3-(4-morpholino)propoxy] quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Octahydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1{[4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] -4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(5-Methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4, -(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(5-methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]amide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2,3,4,5-Tetrahydro-1H-benzoazepin-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimidine;

6-(S-Vinylsulfonamido)-4-(2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl)pyrido[3,4-d]pyrimidine;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(2,3,6,7,8,9-Hexahydro-1H-benzo[g]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1{[4-(2,3-dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]-4--(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(2,3,5,6-Tetrahydropyrrolo[2,3-f]indol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylate;

[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1{[4-(6-methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

[4-(6-Fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-7-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

N-[4-(Quinol-2-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Quinol-2-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(Indol-5-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(Quinol-3-ylamino)quinazolin-6-yl]propynamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]propynamide;

N-[4-(Quinol-3-ylamino)quinazolin-7-yl]propynamide;

N-[4-(Indol-5-ylamino)quinazolin-7-yl]propynamide;

N-[4-(Quinol-5-ylamino)quinazolin-6-yl]but-2-ynamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-ynamide;

N-[4-(Quinol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(Quinol-6-ylamino)quinazolin-6-yl]but-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-enamide;

N-[4-(Quinol-6-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(Quinol-7-ylamino)quinazolin-6-yl]-3-chloroacrylamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(quinol-7-ylamino)quinazoline;

6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(quinol-8-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylamide;

N-[7-[4-(N,N-dimethylamino)butoxy]-4-(quinol-8-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylamide;

N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-6-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-6-ylamino)quinazolin-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1{[4-(indol-5-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(1H-indazol-6-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1H-Indazol-6-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl] amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(4-benzyloxyphenylamino) quinazolin-6-yl]amide;

N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(1H-Indazol-4-ylamino)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid -6-yl]but-2-ynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid -6-yl]but-2-enamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(benzothiazol-5-ylamino)pyrido[3,4-d]-pyrimidine;

6-(S-Vinylsulfonamido)-4-(indol-5-ylamino) pyrido[3,4-d]pyrimidine;

N-[4-(Benzothiazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1{[4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1,2,3,4-Tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1,2,3,4-tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(benzo[c][2,1,3]thiadiazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(Benzo[c][2,1,3]thiadiazol-4-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

[4-(Benzimidazol-5-ylamino)quinazolin-6-yl]acrylate;

[4-(Indol-5-ylamino)quinazolin-6-yl]acrylate;

[4-(Benzimidazol-5-ylamino)quinazolin-7-yl]acrylate;

[4-(Indol-5-ylamino)quinazolin-7-yl]acrylate;

[7-[3-(4-Morpholino)propoxy]-4-(benzimidazol-5-ylamino)quinazolin-6-yl] acrylate;

[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylate;

[7-[4-(N,N-dimethylamino)butoxy]-4-(6-methoxyquinol-8-ylamino)quinazolin-6-yl]acrylate;

[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-methoxyquinol-8-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(indol-5-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1-methylindol-5-ylamino)quinazolin-6-yl]ester;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1{[4-(indol-5-ylamino)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(1-methylindol-5-ylamino)quinazolin-6-yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(2-Methylindol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

7-Morpholin-4-ylhept-2-ynoic acid [4-(3-cyanoindol-5-ylamino)quinazolin-6-yl]ester;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(benzothien-5-ylamino)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]propynamide;

N-[4-(1-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-yl]propynamide;

N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]but-2-ynamide;

N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Benzylindol-6-ylamino)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(1-Benzylindol-6-ylamino)-7-[4-(N,N-dimethylamino)butoxy]-quinazolin-6-yl]acrylamide;

N-[4-(2-Phenylbenzimidazol-5-ylamino)-7-[3-(4-morpholino)propoxy]-quinazolin-6-yl]acrylamide;

N-[4-(2-Phenylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(42-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(3-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(3-Benzylbenzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(1-phenethylbenzindazol-5-ylamino)-pyrido[3,4-d]pyrimidine;

6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)-pyrido[3,4-d]pyrimidine;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzyloxybenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]-pyrimid-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(2-benzylsulfonylbenzimidazol-5-ylamino)-pyrido[3,4-d]pyrimid-6-yl] amidc} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(4-benzyloxybenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl] amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylsulfonylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

N-[4-(1-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester;

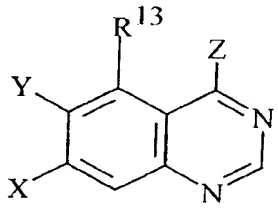
Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate; and

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester.

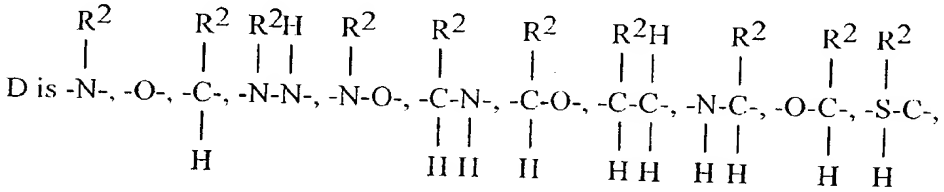
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds having the Formula I

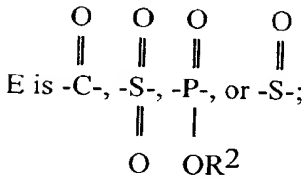


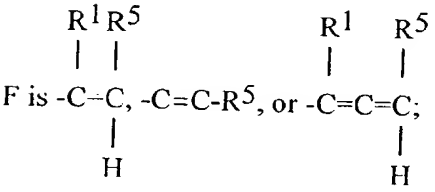
I

wherein X is -D-E-F and Y is $-SR^4$, halogen, $-OR^4$, $-NHR^3$, or hydrogen, or X is $-SR^4$, halogen, $-OR^4$, $-NHR^3$, or hydrogen, and Y is -D-E-F;

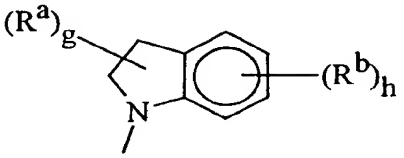


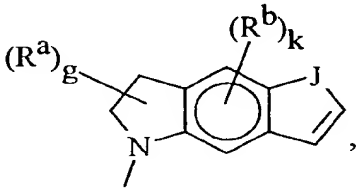
or absent;

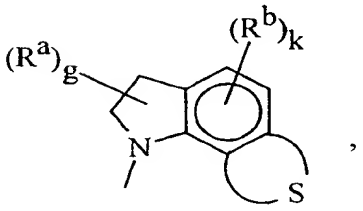


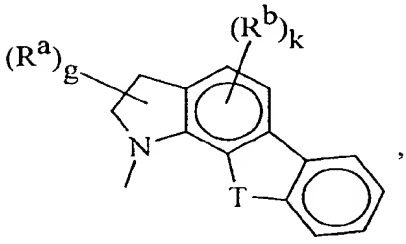


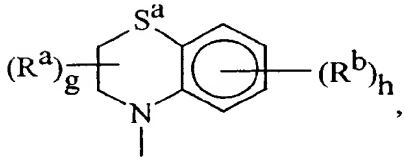
provided that when E is -S- or -S-, D is not -N-C-, or -OC;

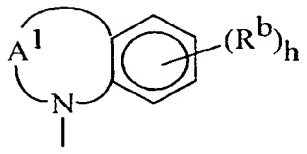
Z is  ,

 ,

 ,

 ,

 ,

 , or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4)alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

each R^b is indcpendently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both cnds to adjacent carbons on the bcnzene moiety, or R^b is -$Z^a R^{77}$;

J is -CH_2-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is -CH_2, -N(H)-, thio, or oxy;

S^a is -CH_2-, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylamino, di-[$(C_1$-$C_4)$alkyl]amino, and $(C_2$-$C_4)$alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-$(C_1$-$C_6)$alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-$(C_1$-$C_6)$alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl;

Z^1, Z^2, or Z^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NH(C_3-C_8 cycloalkyl), -N(C_3-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl,

C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, $-CH_2-$, -S-, SO_2, -NH-, -O-, $-OCH_2-$, $-S-CH_2-$, $-SO_2-$, or $-CH_2CH_2-$;

R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C=CH_2$, $-CH=CH-(C_1-C_6)$alkyl,

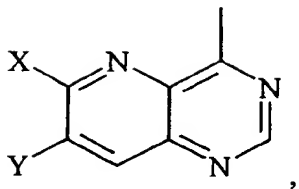
$-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$,$-(CH_2)_nNH(C_1-C_6$alkyl), $-(CH_2)_nN(C_1-C_6$alkyl$)_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from Z^1, Z^2, Z^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above, R^6 is hydrogen or C_1-C_6 alkyl; R^{13} is hydrogen or halogen; and

n is 1 to 4, p is 0 or 1, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In another preferred embodiment, present invention also provides compounds having the Formula II

II

wherein Q is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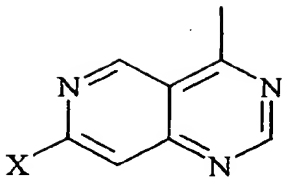
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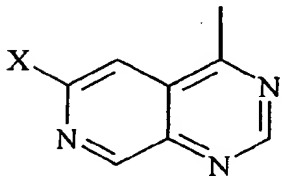
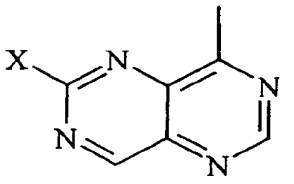
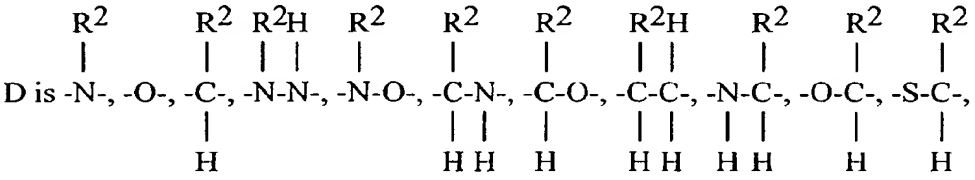
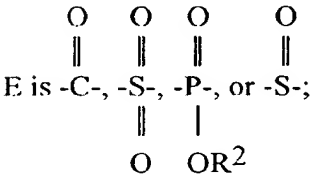
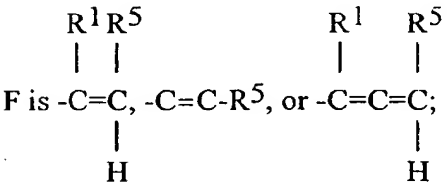

, or

;

p is 0 or 1;

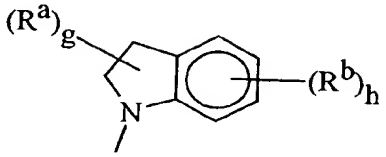
X is -D-E-F, and Y is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;

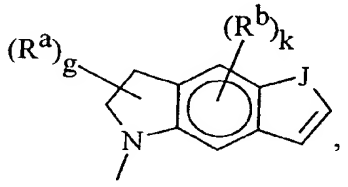
D is 
or absent;

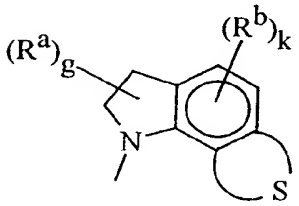
E is 

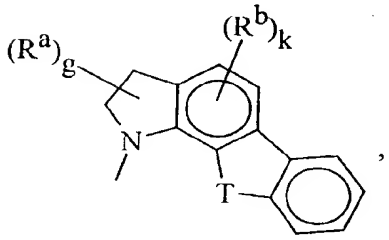
F is 

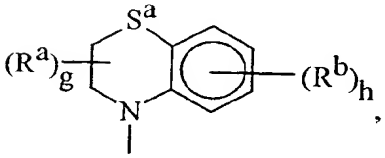
provided that when E is -S- or -S-, D is not -N-C-, or -OC;

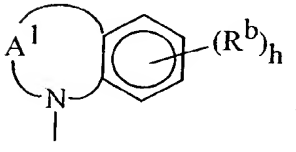
Z is  ,

 ,

 ,

 ,

 ,

 , or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4)alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is $-Z^aR^{77}$;

J is $-CH_2-$, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is $-CH_2$, -N(H)-, thio, or oxy;

S^a is $-CH_2-$, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylamino, di-[$(C_1$-$C_4)$alkyl]amino, and $(C_2$-$C_4)$alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-$(C_1$-$C_6)$alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-$(C_1$-$C_6)$alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl;

E^1, E^2, or E^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NH(C_3-C_8 cycloalkyl), -N(C_3-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl,

C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

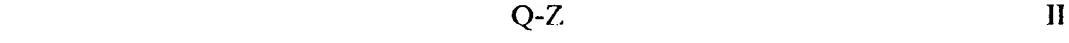
Z^a is a bond, $-CH_2-$, -S-, SO_2, -NH-, -O-, $-OCH_2-$, $-S-CH_2-$, $-SO_2-$, or $-CH_2CH_2-$;

R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C=CH_2$, $-CH=\underset{\displaystyle H}{\underset{|}{C}}-(C_1$-$C_6)$alkyl, $-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$, $-(CH_2)_nNH(C_1$-C_6alkyl), $-(CH_2)_nN(C_1$-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E^1, E^2, E^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above or C_1-C_6 alkyl; and

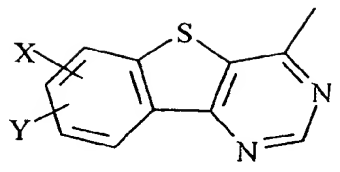
n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In another embodiment, the present invention provides compounds having the Formula II



II

wherein Q is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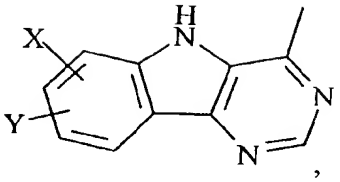
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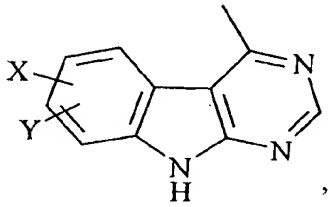
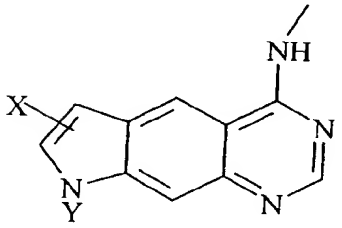
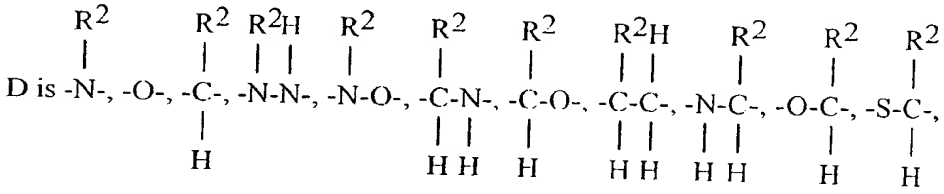
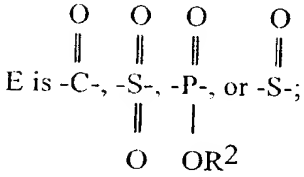
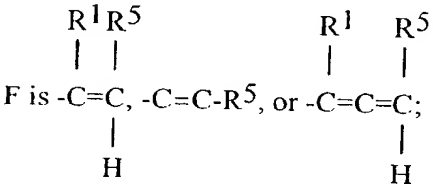

, or

;

p is 0 or 1;

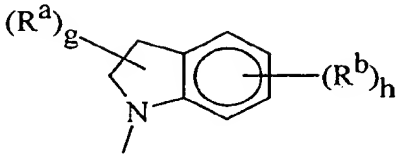
X is -D-E-F, and Y is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;

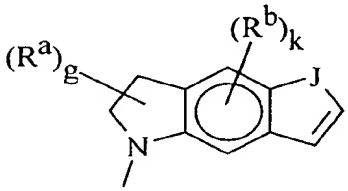
D is  or absent;

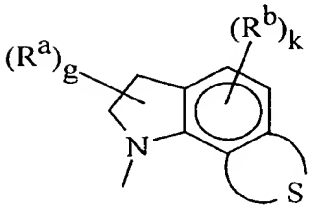
E is  ;

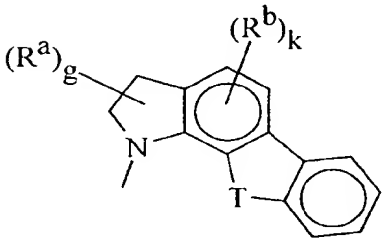
F is 

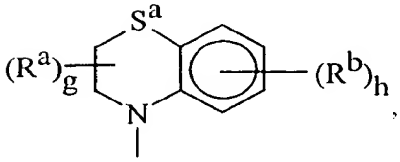
provided that when E is -S- or -S-, D is not -N-C-, or -OC;

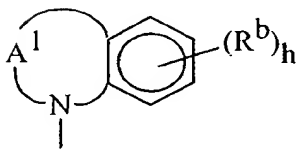
Z is  ,

 ,

 ,

 ,

 ,

 , or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4)alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is -Z^aR^{77};

J is -CH_2-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is -CH_2, -N(H)-, thio, or oxy;

S^a is -CH_2-, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylamino, di-[(C_1-C_4)alkyl]amino, and (C_2-C_4)alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n-N_1$-piperazinyl[$N_4-(C_1-C_6)$alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, $-NH_2$, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_n$OH, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n-N_1$-piperazinyl[$N_4-(C_1-C_6)$alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl;

E^1, E^2, or E^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, $-NH_2$, $-NH(C_1-C_6$ alkyl), $-N(C_1-C_6$ alkyl)$_2$, $-NH(C_3-C_8$ cycloalkyl), $-N(C_3-C_8$ cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl,

C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, $-CH_2-$, -S-, SO_2, -NH-, -O-, $-OCH_2-$, $-S-CH_2-$, $-SO_2-$, or $-CH_2CH_2-$;

R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C(=CH_2)-$, $-CH=CH-(C_1-C_6)$alkyl, $-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$, $-(CH_2)_nNH(C_1-C_6$alkyl), $-(CH_2)_nN(C_1-C_6$alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E^1, E^2, E^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group above in R^5 can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above or C_1-C_6 alkyl; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, sec-butyl, pentyl, and hexyl.

The term "alkoxy" means an alkyl group attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy, and isobutoxy.

The term "halogen" includes chlorine, fluorine, bromine, and iodine.

The term "alkenyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon double bond.

The term "cycloalkyl" means a cyclic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "cycloalkoxy" means a cycloalkyl group attached to an oxygen atom.

The term "perfluoroalkyl" means an alkyl group in which all the hydrogen atoms have been replaced by fluorine atoms.

The term "acyl" means a group derived from an organic acid by removal of the hydroxy group (-OH).

The term "acyloxy" means an acyl group attached to an oxygen atom.

The term "thioalkyl" means an alkyl group attached to a sulfur atom.

The term "sulfinylalkyl" means a sulfinyl group attached to an alkyl group.

The term "sulfonylalkyl" means a sulfonyl group attached to an alkyl group.

The term "thiocycloalkyl" means a cycloalkyl group attached to a sulfur atom.

The term "sulfinylcycloalkyl" means a sulfinyl group attached to a cycloalkyl group.

The term "sulfonylcycloalkyl" means a sulfonyl group attached to a cycloalkyl group.

The term "mercapto" means a -SH group.

The term "alkoxycarbonyl" means an alkoxy group attached to a carbonyl group.

The term "cycloalkoxycarbonyl" means a cycloalkyoxy group attached to a carbonyl group.

The term "cycloalkenyl" means a cyclic hydrocarbon containing one or more carbon-carbon double bond.

The term "alkynyl" means a hydrocarbon having one or more carbon-carbon triple bond.

The term "monocyclic heteroaryl" mean a heterocyclic aryl compound having only one ring structure. The cyclic compound is aromatic and contains one or more heteroatom. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Examples of monocyclic heteroaryl groups include, but are not limited to, pyridyl, thienyl, and imidazoyl.

The symbol "-" represents a covalent bond.

The compounds of Formulas I or II are irreversible inhibitors of tyrosine kinases, particularly EGF tyrosine kinase. A therapeutically effective amount of the compounds of Formula I or II can be administered to a patient having cancer or a patient having restenosis or at risk of having restenosis or a patient having psoriasis, atherosclerosis, or endometriosis. Those skilled in the art are readily able to identify patients having cancer, restenosis, psoriasis, atherosclerosis, or endometriosis, and patients who are at risk of developing restenosis. The term "patient" means animals such as dogs, cats, cows, sheep, and also includes humans.

The compounds of the present invention can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray. The compounds can be administered alone or as part of a pharmaceutically acceptable composition that includes pharmaceutically acceptable excipients. It is noted that more than one compound of Formula I or II can be administered either concurrently or sequentially.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as

ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft- and hard-filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene-glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such

composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic

formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like (see, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J Pharm Sci*, 1977;66:1-19 which is incorporated herein by reference).

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is sufficient. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

The compounds of the present invention can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water,

ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

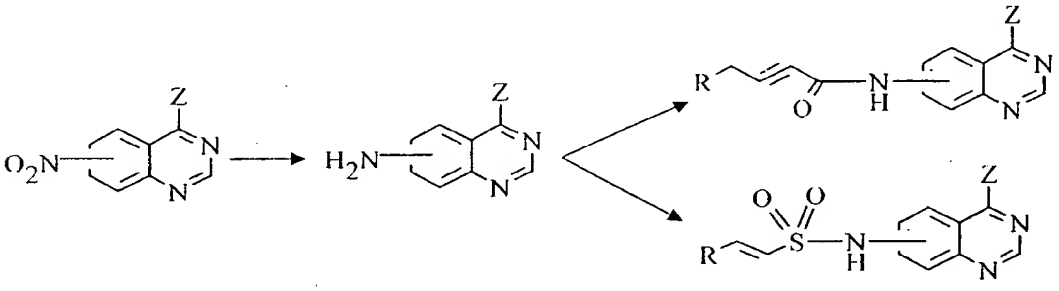
It is intended that the compounds of Formula I, II, or III be either synthetically produced or biologically produced.

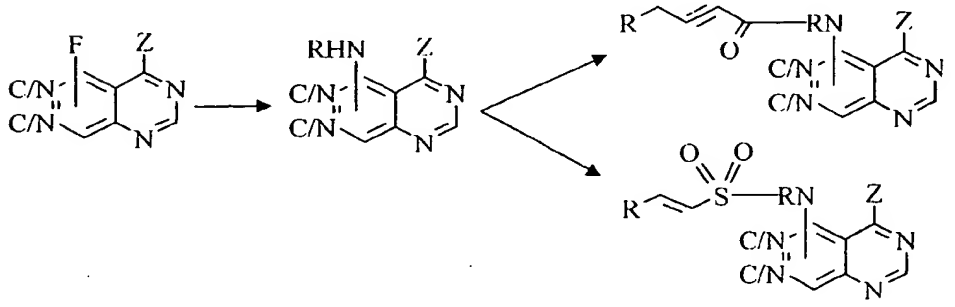
The following examples illustrate particular embodiments of the invention and are not intended to limit the specification, including the claims, in any manner.

GENERAL SYNTHETIC SCHEMES

Amine-Linked Alkylating Michael Acceptor Sidechains

The amine is acylated either by an acid in the presence of a coupling agent such as EDAC, or by an acid chloride. The amine in turn can be made by reduction of the corresponding nitro compound, displacement of a halogen by an amine or ammonia equivalent, or in the case of pyrido[4,3-d]pyrimidines by direct incorporation during the synthesis. 2-Haloalkylsulfonyl halides form vinyl sulfonamides when treated with the aryl amine and excess tertiary amine base.



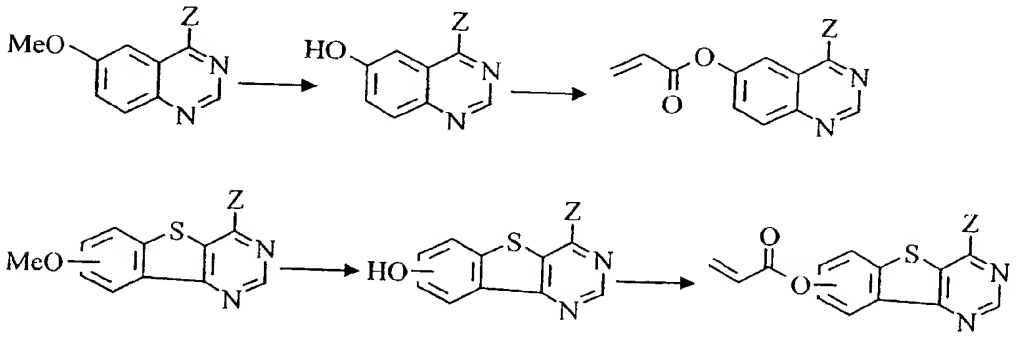


C/N means either a carbon or nitrogen atom is present at that location.

--- means a bond or no bond.

Oxygen-Linked Alkylating Michael Acceptor Sidechains

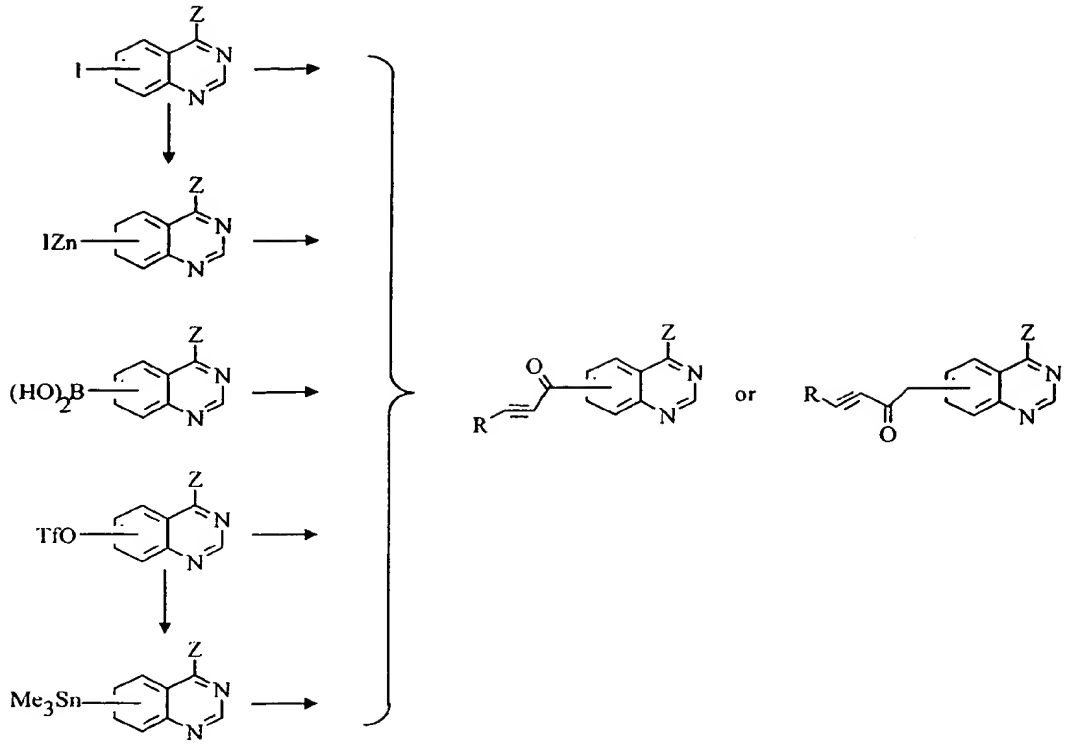
The hydroxyl group is acylated either by an acid in the presence of a coupling agent such as EDAC, or by an acid chloride. The hydroxyl compound can in turn can be made by cleavage of the corresponding methyl ether. 3-Methylthioalkanoic acid or their acid chlorides can be used to acylate the oxygen followed by S-alkylation or oxidation and basic or thermal elimination.



Ar and R denote an aryl group and R denotes an organic group as exemplified herein.

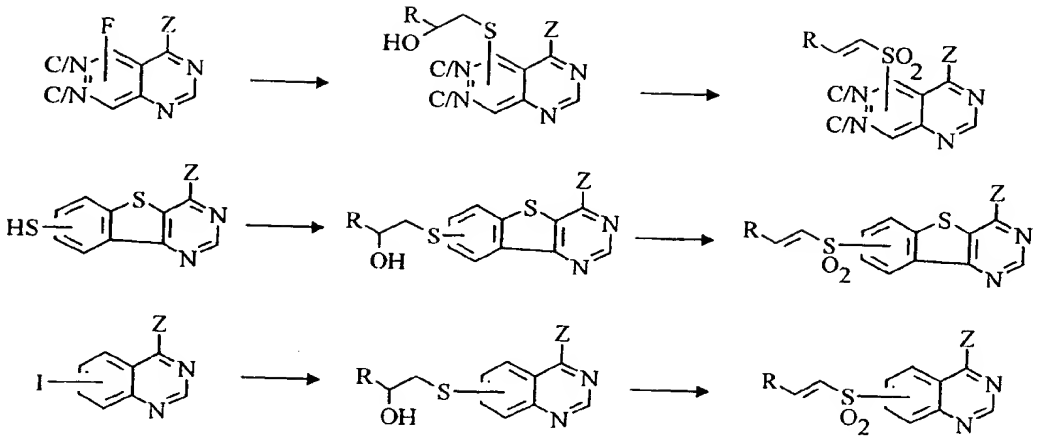
Carbon-Linked Alkylating Michael Acceptor Sidechains

A Stille or Suzuki coupling can be used to couple the sidechain to an appropriately substituted quinazoline/pyridopyrimidine/pyrimidinopyrimidine/ tricycle. These in turn can be made as aryl halides by methods known in the art, or as aryl triflates by triflation of the hydroxyl compounds described above, as aryl stannanes by reaction of the abovementioned triflates with hexamethyl distannane, or as arylboronic acids by conversion of aryl iodides to arylorgano-metallics, followed by treatment with borate esters and hydrolysis. Alternatively, aryl iodides can be converted to the arylzinc species and coupled with activated halides.



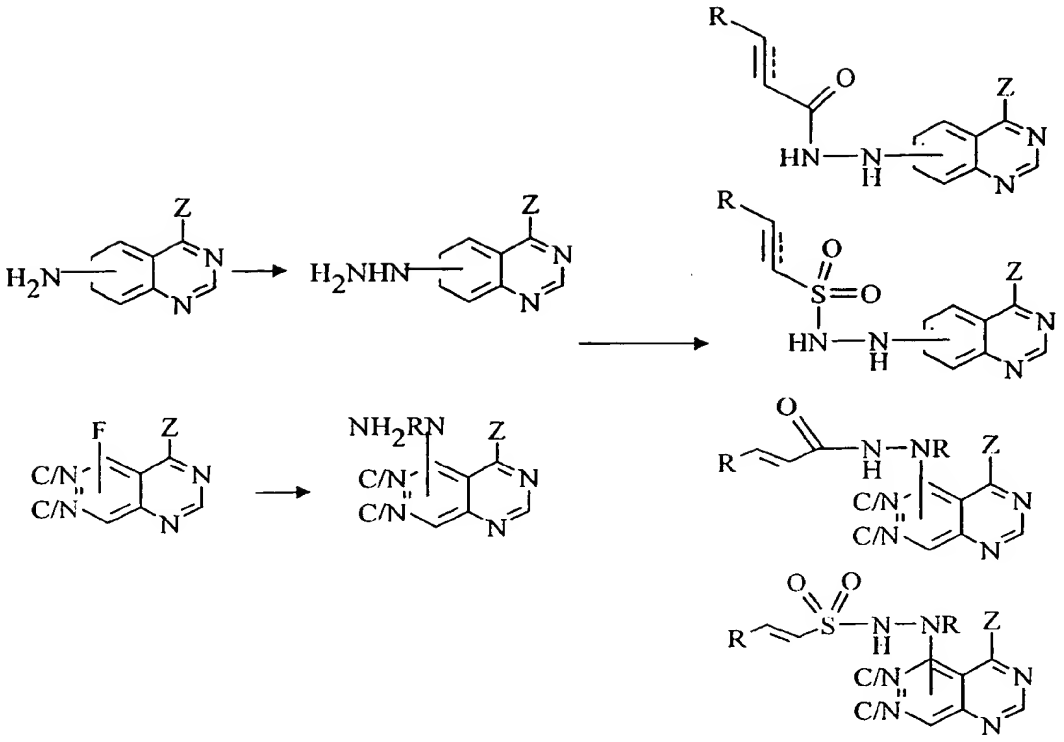
Sulfur-Linked Alkylating Michael Acceptor Sidechains

Activated halides in pyridopyrimidines and pyrimidinopyrimidines can be displaced by suitable 2-hydroxythiolates, and these in turn can be oxidized to sulfones, and then water eliminated by treatment with mesyl chloride and several equivalents of a base. For quinazolines, and claimed tricycles, either an activated halogen especially fluorine can be used in the sequence just described for pyridopyrimidines, or an aryl iodide precursor can be metalated, quenched with sulfur or a suitable sulfur electrophilic progenitor and then the resultant aryl thiol used to open a terminal epoxide, giving a 2-hydroxy thioether which can be converted onto a vinyl sulfone by oxidation and water elimination as described above.



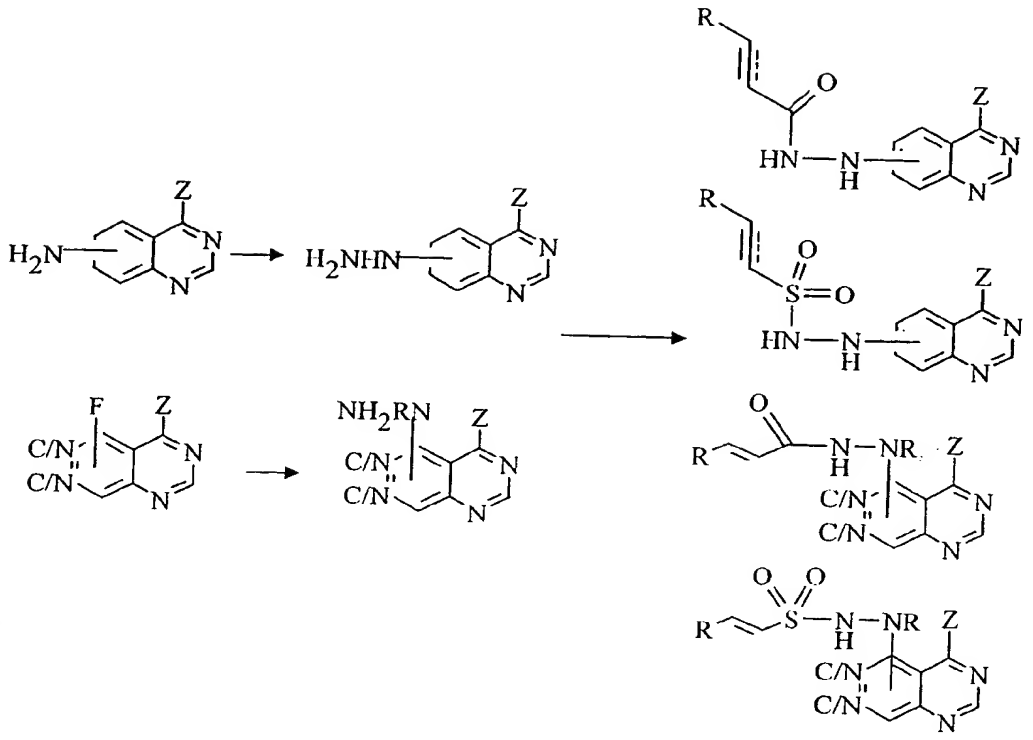
Hydrazino-Linked Alkylating Michael Acceptor Sidechains

Activated halides in pyridopyrimidines and pyrimidinopyrimidines and appropriately substituted quinazolines can be displaced by a (N-alkyl) hydrazine. Alternatively, an amino-derivative of the desired ring nucleus can be diazotized, and then reduced to the hydrazine. The distal nitrogen of the hydrazine can then be acylated, sulfonylated or phosphorylated, by methods well-known to one skilled in the art.



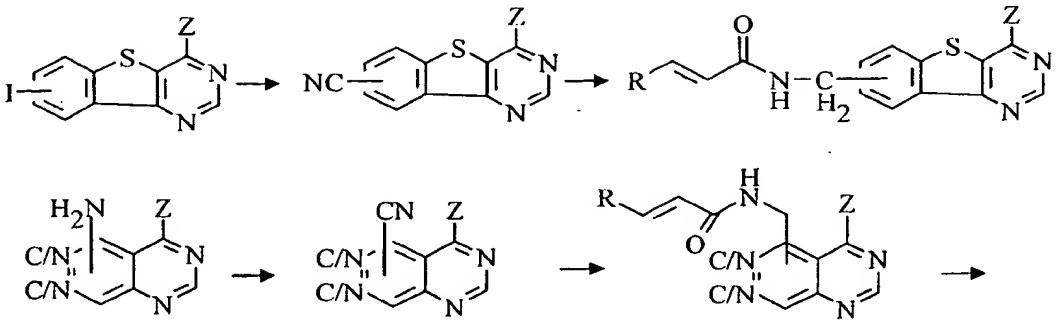
Hydroxylamino-O-Linked Alkylating Michael Acceptor Sidechains

Activated halides in pyridopyrimidines and pyrimidinopyrimidines and appropriately substituted quinazolines can be displaced by a suitably O-protected (N-alkyl) hydroxylamine. Alternatively, a nitro-derivative of the desired ring nucleus can be synthesized, and then reduced to the hydroxylamine under appropriate mildly reducing conditions. The oxygen of the hydroxylamine can then be acylated, sulfonylated or phosphorylated, by methods well-known to one skilled in the art.



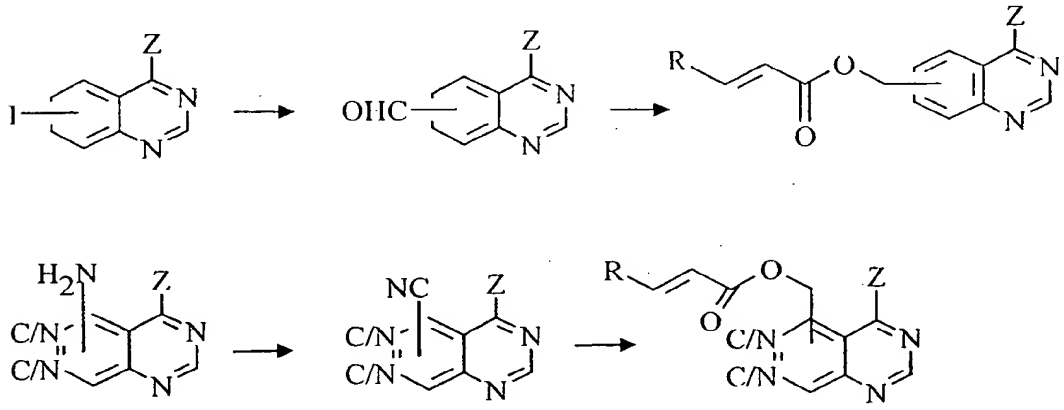
Methyleneamino-N-Linked Alkylating Michael Acceptor Sidechains

Activated halides in pyridopyrimidines and pyrimidinopyrimidines and appropriately substituted quinazolines can be displaced by cyanide, preferably in the presence of copper or nickel salt catalysis. Alternatively, an amino-derivative of the desired ring nucleus can be diazotized, and then converted to the nitrile as described above. In some cases, the nitrile functionality can be incorporated into the heterocycle earlier in the synthesis, either as itself, or via a carboxylic acid or aldehyde, both of which can readily be turned into nitrile compounds by one skilled in the art. Reduction of the nitrile to a methyleneamine is followed by nitrogen acylation, sulfonylation or phosphorylation, by methods well-known to one skilled in the art.



Methyleneoxy-O-Linked Alkylating Michael Acceptor Sidechains

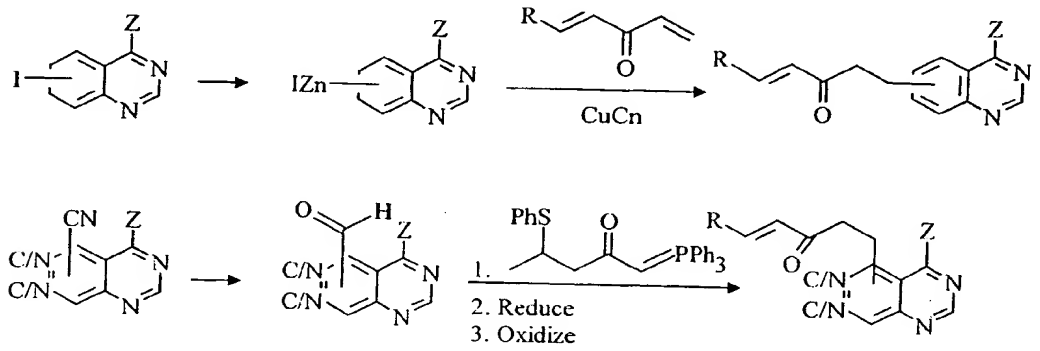
Hydroxymethyl compounds can be incorporated into appropriate heterocycles in many ways obvious to one skilled in the art. For example, iodoquinazolines may be carbonylated in a Heck reaction, and then reduced with $NaBH_4$ to the desired precursor. Aminopyridopyrimidines may be diazotized, converted to the nitrile, partially reduced to an imine, hydrolysed, and the resultant aldehyde reduced to hydroxymethyl. The oxygen of the hydroxymethyl can then be acylated, sulfonylated or phosphorylated, by methods well-known to one skilled in the art.



Ethano-Linked Alkylating Michael Acceptor Sidechains

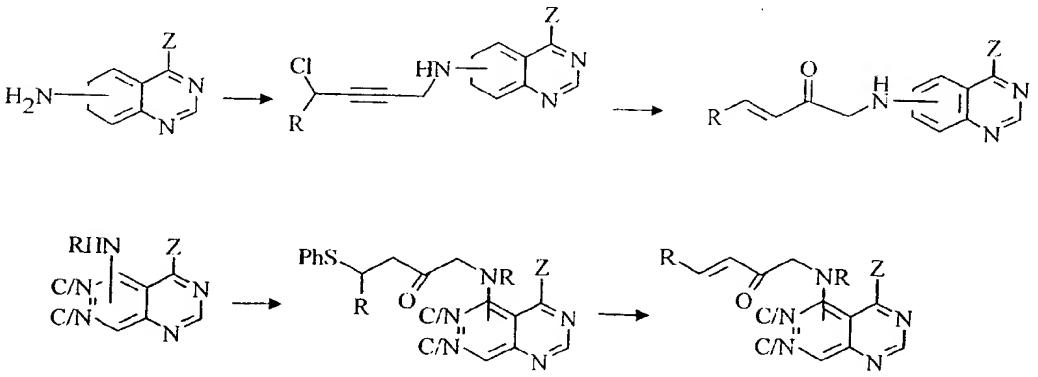
Michael addition of a cuprate, derived via an organozincate from an iodoquinazoline, to a divinylketone, or appropriately mono-masked derivative, followed by unmasking of the second unsaturated functionality, if required, will give compounds of the desired type. Aldehydes derived from pyridopyrimidines or

pyrimidopyrimidnes as described above can be homologated to the desired compounds by a wide variety of techniques such as the one illustrated, by one skilled in the art.



Aminomethyl-C-Linked Alkylating Michael Acceptor Sidechains

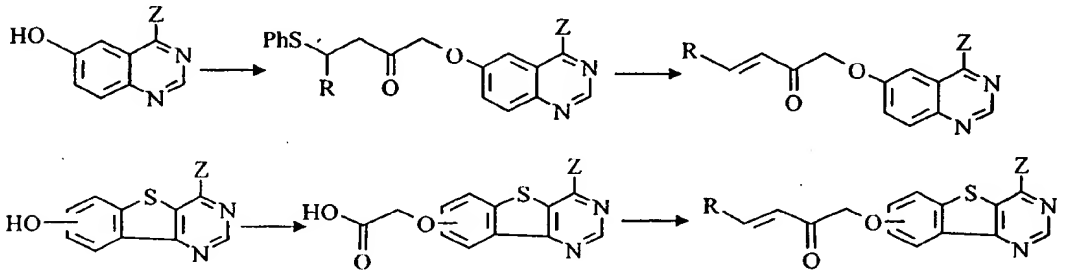
Amino-heterocycles of the type described throughout this application can be alkylated by various double bond-masked equivalents of 1-bromobut-3-en-2-one, followed by unmasking of the unsaturation by methods known to one skilled in the art.



Hydroxymethyl-C-Linked Alkylating Michael Acceptor Sidechains

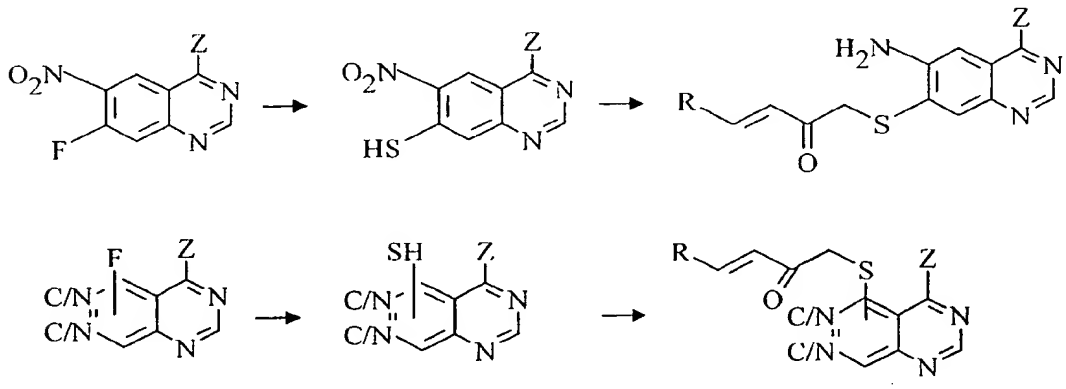
Hydroxy-heterocycles made as described previously from methoxy-heterocycles can be alkylated by various double bond-masked equivalents of 1-bromobut-3-en-2-one, followed by unmasking of the unsaturation by methods known to one skilled in the art. Alternatively, alkylation of the phenol can be

accomplished with chloroacetic acid, followed by conversion to an acyl chloride and Stille coupling of that acyl halide with an appropriate alkenyl stannane.



Thiomethyl-C-Linked Alkylating Michael Acceptor Sidechains

Appropriate mercapto-heterocycles, made by displacement of activated halides on the heteroaromatic ring, can be alkylated by various double bond-masked equivalents of 1-bromobut-3-en-2-one, followed by unmasking of the unsaturation by methods known to one skilled in the art. Alternatively, alkylation of the thiol can be accomplished with chloroacetic acid, followed by conversion to an acyl chloride and Stille coupling of that acyl halide with an appropriate alkenyl stannane.



EXAMPLE 1

N-[4-(6-Bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide

Step (a) 6-Nitro-4-(1-(6-bromo-indolinyl))-quinazoline

A suspension of 6-bromo-indoline (490 mg, 2.47 mmol) (Miyake Y., Kikugawa Y., *J. Het. Chem.*, 1983;20:349), 4-chloro-6-nitro-quinazoline (660 mg,

2.47 mmol), and N,N-dimethylaniline (0.63 mL, 4.9 mmol) in 15 mL of isopropyl alcohol was heated under reflux for 1 hour. The suspension was concentrated to give a solid, which was shaken with a mixture of ethyl acetate and saturated aqueous sodium bicarbonate. The solid was collected by filtration and recrystallized from a boiling mixture of ethanol (100 mL) and dimethylformamide (25 mL) to give the product as a yellow solid (290 mg, 32%), mp 249-251°C.

Anal. Calcd. for $C_{16}H_{11}Br_1N_4O_2$:

C, 51.77; H, 2.99; N, 15.09.

Found: C, 51.58; H, 2.91; N, 15.01.

MS (APCI): Calcd. for M + 1, 371.0; Found, 371.0

Step (b) 6-Amino-4-(1-(6-bromo-indolinyl))-quinazoline

To a suspension of 6-nitro-4-(1-(6-bromo-indolinyl))-quinazoline (240 mg, 6.5 mmol) and acetic acid (1.04 mL, 18 mmol) in H_2O (75 mL) and ethanol (100 mL), heated under reflux, was added iron powder (washed with 1N HCl, then H_2O, and dried; 180 mg, 3.23 mmol). After 30 minutes of heating, more iron powder (320 mg, 5.73 mmol) was added, and heating was continued for another 30 minutes. The reaction was filtered while hot and the solids washed with ethanol. To the filtrate and washings was added concentrated NH_4OH (10 mL), and a small amount of solid was removed by filtration. The filtrate was concentrated, and the resulting residue was purified by flash silica gel chromatography dichloromethane/methanol, 10:1) to give a yellow foam.

MS (APCI): Calcd. for $C_{16}H_{13}Br_1N_4$: M + 1, 341.0; Found, 341.1

The NMR spectrum showed the presence of an acetate species. This was removed by dissolving the solid in diethylether, and washing the solution consecutively with H_2O, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$) and concentrated to give the product as a brown solid (220 mg, 100%).

Step (c)

To a suspension of 6-amino-4-(1-(6-bromo-indolinyl))-quinazoline (200 mg, 0.6 mmol) and N-ethyl-N'-(3-N,N-dimethylaminopropylcarbodiimide hydrochloride) (450 mg, 2.3 mmol) in dimethylformamide (1 mL) and tetrahydrofuran (3 mL), cooled in an ice-bath and under nitrogen, was added acrylic acid (0.16 mL, 2.3 mmol), followed by diisopropylethylamine (0.40 mL, 2.3 mmol). The ice-bath was removed, and the suspension was stirred at room temperature for 18 hours. The resulting solution was poured into cold H_2O, and the suspension was extracted with dicholoromethane (4 × 25 mL). The extracts were dried ($MgSO_4$), concentrated, and purified by flash silica gel chromatography (dichloromethane/methanol, 9:1) to give the product as a light yellow solid (110 mg, 41%), mp 214-216°C. This material contained 0.3 mol of dimethylformamide (substantiated by NMR) and 0.3 mol H_2O by C,H,N analysis.

Anal. Calcd. for $C_{19}H_{15}Br_1N_4O_1 \cdot 0.3DMF \cdot 0.3H_2O$:

C, 56.56; H, 4.22; N, 14.25.

Found: C, 56.37; H, 4.14: N, 14.01.

MS (APCI): Calcd. for M + 1, 395.0; Found, 395.1

BIOLOGICAL METHODS

Tissue Culture

A431 human epidermoid carcinoma cells were obtained from the American Type Culture Collection, Rockville, MD and maintained as monolayers in dMEM (Dulbecco's modified eagle medium)/F12, 50:50 (Gibco/BRL) containing 10% fetal bovine serum. For growth inhibition assays, dilutions of the designated compound in 10 µL were placed in 24-well Linbro plates (1.7 × 1.6 cm, flat bottom) followed by the addition of cells (2×10^4) in 2 mL of media. The plates were incubated for 72 hours at 37°C in a humidified atmosphere containing 5% CO_2 in air. Cell growth was determined by cell count with a Coulter Model AM electronic cell counter (Coulter Electronics, Inc., Hialeah, FL).

Purification of Epidermal Growth Factor Receptor Tyrosine Kinase

Human EGF receptor tyrosine kinase was isolated from A431 human epidermoid carcinoma cells by the following method. Cells were grown in roller bottles in dMEM/F12 media (Gibco/BRL) containing 10% fetal calf serum. Approximately 10^9 cells were lysed in 2 volumes of buffer containing 20 mM N-[2-hydroxyethyl]piperazine-N'-[2-ethane sulfonic acid](Hepes), pH 7.4, 5 mM ethylene glycol-bis(β-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1% Triton X-100, 10% glycerol, 0.1 mM sodium orthovanadate, 5 mM sodium fluoride, 4 mM pyrophosphate, 4 mM benzamide, 1 mM dithiothreitol (DTT), 80 μg/mL aprotinin, 40 μg/mL leupeptin, and 1 mM phenylmethyl sulfonyl fluoride (PMSF). After centrifugation at 25,000 × g for 10 minutes, the supernatant was applied to a fast Q sepharose column (Pharmacia Biotech., Inc., Piscataway, NJ) and eluted with a linear gradient from 0.1 M NaCl to 0.4 M NaCl in 50 mM Hepes, 10% glycerol, pH 7.4. Enzyme active fractions were pooled, divided into aliquots, and stored at -100°C. Fibroblast growth factor receptor (FGFR), platelet-derived growth factor (PDGF), insulin, and c-src tyrosine kinases were obtained by methods well-known in the art. For example, see Fry et al., "Strategies For The Discovery Of Novel Tyrosine Kinase Inhibitors With Anticancer Activity, *Anticancer Drug Design*, 1994;9:331-351.

Tyrosine Kinase Assays

Enzyme assays for IC_{50} determinations were performed in 96-well filter plates (Millipore MADVN6550, Millipore, Bedford, MA). The total volume was 0.1 mL containing 20 mM Hepes, pH 7.4, 50 μM sodium vanadate, 40 mM magnesium chloride, 10 μM adenosine triphosphate (ATP) containing 0.5 μCi of [^{32}P]ATP, 20 μg of poly Glutamic acid/tyrosine (Sigma Chemical Co., St. Louis, MO), 10 ng of EGF receptor tyrosine kinase and appropriate dilutions of inhibitor. All components except the ATP are added to the well and the plate incubated with shaking for 10 minutes at 25°C. The reaction is started by adding [^{32}P]ATP, and the plate is incubated at 25°C for 10 minutes. The reaction is terminated by

addition of 0.1 mL of 20% trichloroacetic acid (TCA). The plate is kept at 4°C for at least 15 minutes to allow the substrate to precipitate. The wells are then washed 5 times with 0.2 mL of 10% TCA and ^{32}P incorporation determined with a Wallac beta plate counter (Wallac, Inc., Gaithersburg, PA). Assays using intracellular kinase domains of PDGF, FGF, and insulin receptors, as well as those for c-src, were performed as described for the EGF receptor except that 10 mM Manganese chloride was included in the reaction.

Western Blotting Procedure

Extracts were made by lysing the monolayers in 0.2 mL of boiling Laemlli buffer (2% sodium dodecyl sulfate, 5% beta-mercaptoethanol, 10% glycerol and 50 mM tris[hydroxymethyl]aminomethane (Tris), pH 6.8), and the lysates were heated to 100°C for 5 minutes. Proteins in the lysate were separated by polyacrylamide gel electrophoresis and electrophoretically transferred to nitrocellulose. The membrane was washed once in 10 mM Tris, pH 7.2, 150 mM NaCl, 0.01% Azide (TNA), and blocked overnight in TNA containing 5% bovine serum albumin and 1% ovalbumin. The membrane was blotted for 2 hours with antiphosphotyrosine antibody (UBI, 1 µg/mL in blocking buffer) and then washed twice in TNA, once in TNA containing 0.05% Tween-20 detergent and 0.05% nonidet P-40 detergent and twice in TNA. The membranes were then incubated for 2 hours in blocking buffer containing 0.1 µCi/mL of [^{125}I]protein A and then washed again as above. After the blots were dry, they were loaded into a film cassette and exposed to X-AR X-ray film (Eastman Kodak Co., Rochester, NY) for 1 to 7 days. Band intensities were determined with a Molecular Dynamics laser densitometer.

Autophosphorylation Assay

A431 human epidermoid carcinoma cells were grown in 6-well plates to about 80% confluency and then incubated in serum-free media for 18 hours. Duplicate sets of cells were treated with a range of concentrations of the designated compound to be tested as an inhibitor for 15 minutes. The cells were

then stimulated with 100 ng/mL of EGF for 5 minutes and extracts made as described under the Western Blotting Procedure.

Irreversibility Test Protocol

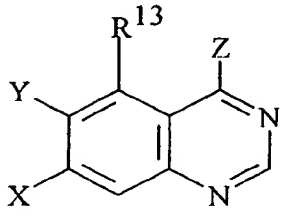
A431 human epidermoid carcinoma cells were grown in 6-well plates to about 80% confluency and then incubated in serum-free media for 18 hours. Duplicate sets of cells were treated with 2 μM of designated compound to be tested as an irreversible inhibitor for either 1 or 2 hours. One set of cells was then stimulated with 100 ng/mL of EGF for 5 minutes and extracts made as described under the western blotting procedure. The other set of cells were washed free of the compound with warmed serum-free media, incubated for 2 hours, washed again, incubated another 2 hours, washed again, and then incubated a further 4 hours. This set of cells was then stimulated with EGF and extracts made similar to the first set of cells.

Example Number	IC_{50} (nM) EGFr (isolated enzyme assay)	IC_{50} (nM) A431 Cell Autophosphorylation Assay	Irreversibility Test
1	0.4	9.9	yes, irreversible

CLAIMS

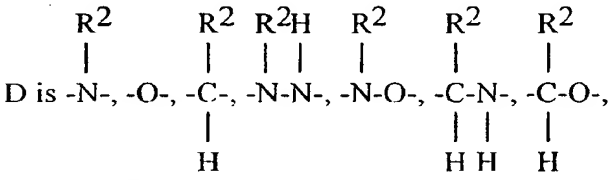
What is claimed is:

1. A compound having the Formula I

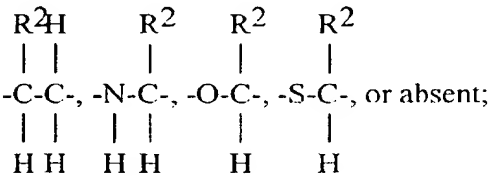


I

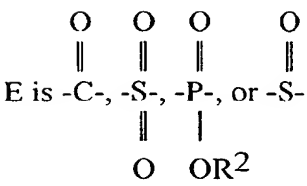
wherein X is -D-E-F and Y is $-SR^4$, halogen, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, halogen, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;



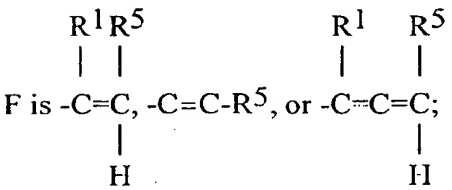
D is -N-, -O-, -C-, -N-N-, -N-O-, -C-N-, -C-O-,



-C-C-, -N-C-, -O-C-, -S-C-, or absent;

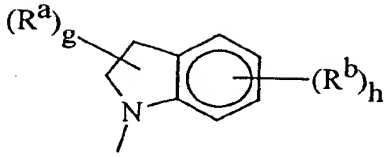


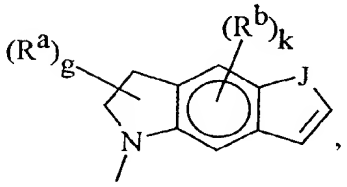
E is -C-, -S-, -P-, or -S-;

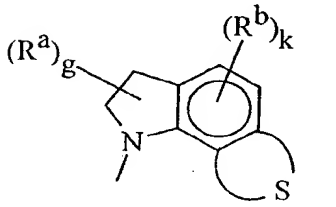


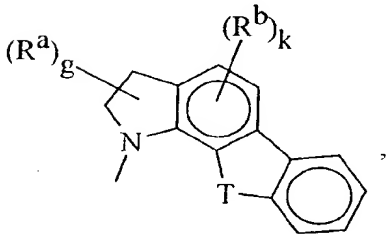
F is -C=C, -C=C-R^5, or -C=C=C;

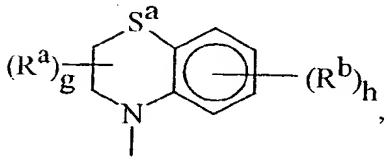
provided that when E is -S- or -S-, D is not -N-C-, or -OC;

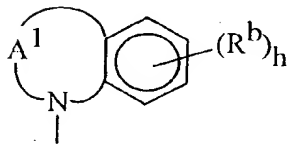
Z is  ,

 ,

 ,

 ,

 ,

 , or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4) alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally monosubstituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is $-Z^aR^{77}$;

J is $-CH_2-$, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is $-CH_2$, -N(H)-, thio, or oxy;

S^a is $-CH_2$-, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkylamino, di-[$(C_1$-$C_4)$alkyl]amino, and $(C_2$-$C_4)$alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-$(C_1$-$C_6)$alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_n$OH, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-$(C_1$-$C_6)$alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl;

Z^1, Z^2, or Z^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NH(C_3$-C_8 cycloalkyl), $-N(C_3$-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl, C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

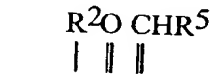
Z^a is a bond, $-CH_2$-, -S-, SO_2, -NH-, -O-, $-OCH_2$-, $-S-CH_2$-, $-SO_2$-, or $-CH_2CH_2$-;

R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C{=}CH_2$, $-CH{=}CH-(C_1$-$C_6)$alkyl, $-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$,$-(CH_2)_nNH$ (C_1-C_6alkyl), $-(CH_2)_nN(C_1$-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from Z^1, Z^2, Z^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

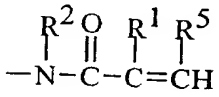
2. A compound of Claim 1 wherein



X is -N-C-C-R^1, and Y is hydrogen, or

X is hydrogen, and Y is -N-C-C-R^1.

3. A compound of Claim 1 wherein Y is -D-E-F and -D-E-F is



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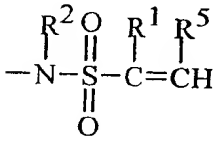
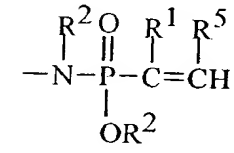
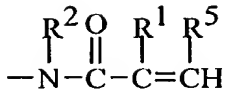


, or



4. A compound of Claim 1 wherein X is -D-E-F and -D-E-F is



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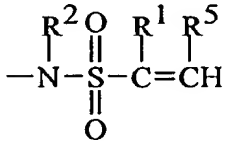

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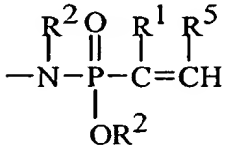


.

5. A compound of Claim 3 wherein R^2 is hydrogen.

6. A compound of Claim 4 wherein R^2 is hydrogen.

7. A compound of Claim 3 wherein R^2 is -$(CH_2)_n$-morpholino.

8. A compound of Claim 4 wherein R^2 is -$(CH_2)_n$-morpholino.

9. A compound of Claim 3 wherein R^5 is carboxy, (C_1-C_6)alkyloxycarbonyl or C_1-C_6 alkyl.

10. A compound of Claim 1 wherein Y is -D-E-F, and X is -O-$(CH_2)_n$-morpholino.

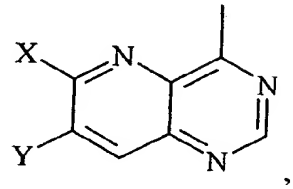
11. A compound of Claim 1 wherein Y is -D-E-F, and X is -O-$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl].

12. A compound of Claim 1 wherein Y is -D-E-F and X is -O-$(CH_2)_n$-imidazoyl.

13. A compound having the Formula II

Q-Z II

wherein Q is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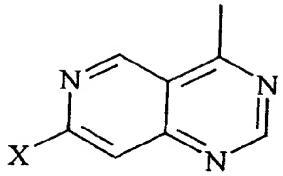
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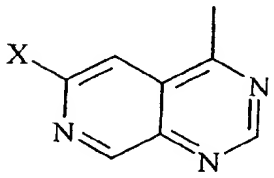
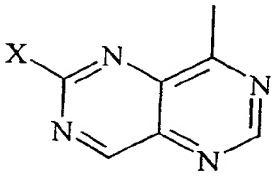
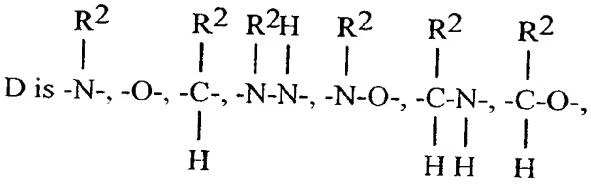
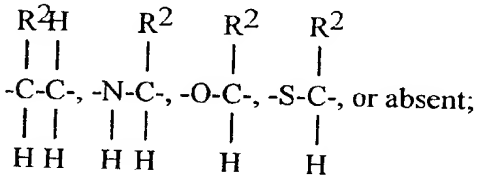
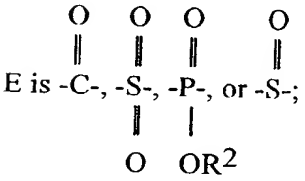

, or

;

X is -D-E-F and Y is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;

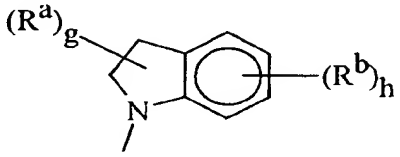


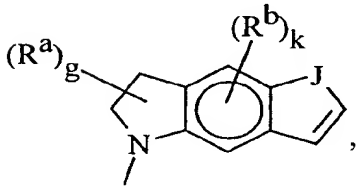


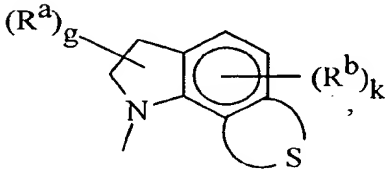


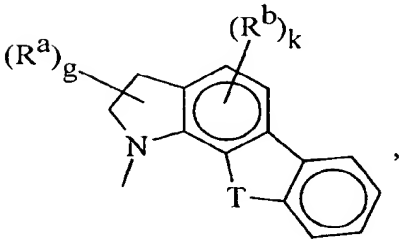
F is -C=C, -C=C-R^5, or -C=C=C;

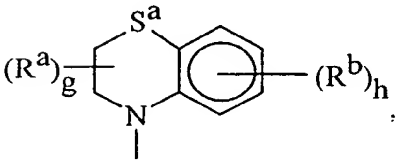
provided that when E is -S- or -S-, D is not -N-C-, or -OC;

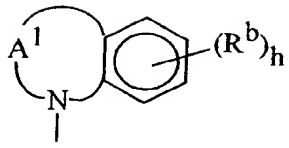
Z is  ,

 ,

 ,

 ,

 .



, or —NH—Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4) alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally monosubstituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is -Z^aR^{77};

J is -CH_2-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is $-CH_2$, -N(H)-, thio, or oxy;

S^a is $-CH_2-$, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen hetcroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylamino, di-$[(C_1-C_4)$alkyl]amino, and (C_2-C_4)alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n-N_1$-piperazinyl[$N_4-(C_1-C_6)$alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, NH_2, or $-N(A)-B$, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_nOH$, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl,

$-(CH_2)_n-N_1$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl;

E^1, E^2, or E^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NH(C_3$-C_8 cycloalkyl), $-N(C_3$-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl, C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, $-CH_2$-, -S-, SO_2, -NH-, -O-, $-OCH_2$-, $-S-CH_2$-, $-SO_2$-, or $-CH_2CH_2$-;

R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)$n-N-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-C{=}CH_2$, $-CH{=}CH-(C_1$-$C_6)$alkyl,

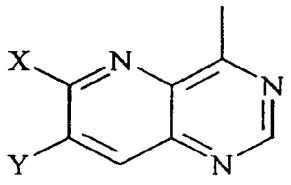
$$\begin{array}{c} \\ | \\ H \end{array}$$

$-(CH_2)_n$-N-hexahydroazepine, $-(CH_2)_nNH_2$,$-(CH_2)_nNH$ (C_1-C_6alkyl), $-(CH_2)_nN(C_1$-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E^1, E^2, E^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl

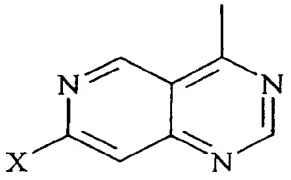
group can be substituted with -OH, $-NH_2$ or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

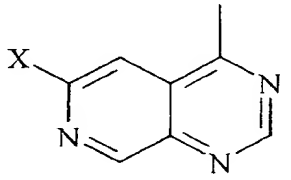
14. A compound of Claim 13 wherein Q is



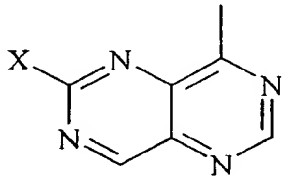
15. A compound of Claim 13 wherein Q is



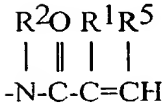
16. A compound of Claim 13 wherein Q is



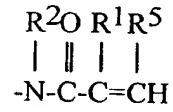
17. A compound of Claim 13 wherein Q is



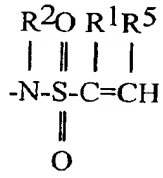
18. A compound of Claim 15 wherein X is



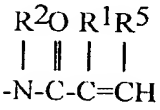
19. A compound of Claim 16 wherein X is



20. A compound of Claim 16 wherein X is



21. A compound of Claim 14 wherein X is

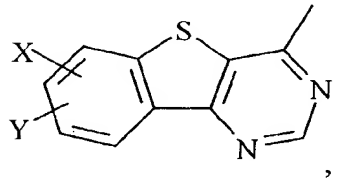


and Y is hydrogen.

22. A compound having the Formula II

II

wherein Q is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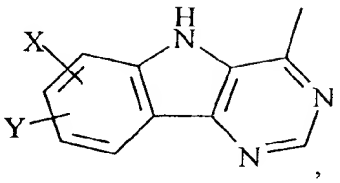
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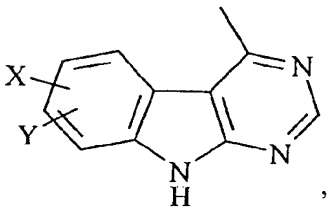
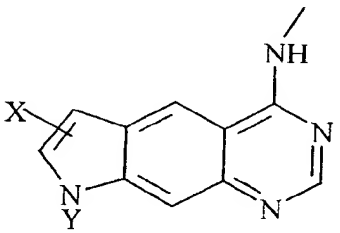

, or

;

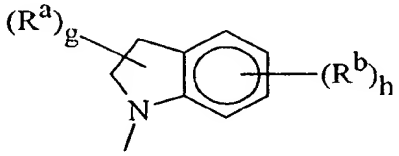
X is -D-E-F and Y is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, or X is $-SR^4$, $-OR^4$, $-NHR^3$ or hydrogen, and Y is -D-E-F;

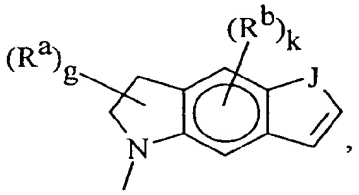
D is -N-, -O-, -C-, -N-N-, -N-O-, -C-N-, -C-O-, -C-C-, -N-C-, -O-C-, -S-C-, or absent;

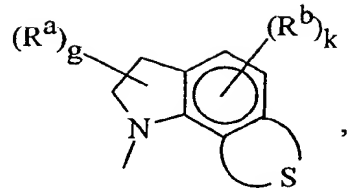
E is -C-, -S-, or -P-;

F is -C=C, $-C=C-R^5$, or -C=C=C;

provided that when E is -S- or -S-, D is not -N-C-, or -OC;

Z is  ,

 ,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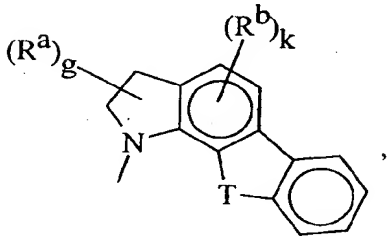
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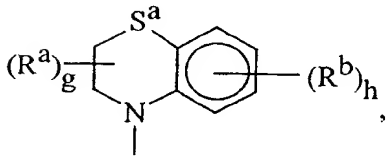
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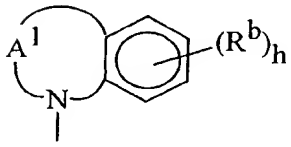

, or —NH— Q^a ;

each R^a is independently hydroxy, amino, N-mono- or N,N-di-(C_1-C_4) alkylamino, sulfo, or (C_1-C_4)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R^a is independently carboxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4) alkyl, amino(C_1-C_4)alkyl, mono-N- or di-N,N-(C_1-C_4) alkylamino(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, 4-(C_1-C_4)alkyl-piperazin-1-yl(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl, sulfo(C_1-C_4)alkyl or (C_1-C_4)alkyl;

each R^b is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C_1-C_4)alkyl, phenyl, thienyl, (C_1-C_4)alkoxy, benzyloxy, phenoxy, (C_2-C_6)alkenyl,

(C_2-C_6)alkynyl, (C_1-C_4)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyl, N-mono- or N,N-di-(C_1-C_4)alkylamino, (C_1-C_4)alkylsulfonylamino, trifluoromethylsulfonylamino, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl or (C_1-C_4)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally monosubstituted with halo, nitro, trifluoromethyl, hydroxy, or (C_1-C_4)alkyl and said (C_1-C_4)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R^b is $-Z^aR^{77}$;

J is $-CH_2-$, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

T is $-CH_2$, -N(H)-, thio, or oxy;

S^a is $-CH_2-$, oxy, or thio;

A^1 completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q^a is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q^a is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylamino, di-[(C_1-C_4)alkyl]amino, and (C_2-C_4)alkanoylamino;

R^1 is hydrogen, halogen, or C_1-C_6 alkyl;

R^2, R^3, and R^4 are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl;

E^1, E^2, or E^3 are independently hydrogen, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, nitro, C_1-C_6 perfluoroalkyl, hydroxy, C_1-C_6 acyloxy, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NH(C_3-C_8 cycloalkyl), -N(C_3-C_8 cycloalkyl)$_2$, hydroxymethyl, C_1-C_6 acyl, cyano, azido, C_1-C_6 thioalkyl, C_1-C_6 sulfinylalkyl, C_1-C_6 sulfonylalkyl, C_3-C_8 thiocycloalkyl, C_3-C_8 sulfinylcycloalkyl, C_3-C_8 sulfonylcycloalkyl, mercapto, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkoxycarbonyl, C_2-C_4 alkenyl, C_4-C_8 cycloalkenyl, or C_2-C_4 alkynyl;

Z^a is a bond, -CH_2-, -S-, SO_2, -NH-, -O-, -OCH_2-, -S-CH_2-, -SO_2-, or -CH_2CH_2-;

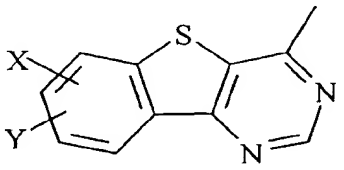
R^{77} is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

R^5 is hydrogen, halogen, C_1-C_6 perfluoroalkyl, 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -(CH_2)n-N-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -C=CH_2, -CH=CH-(C_1-C_6)alkyl,

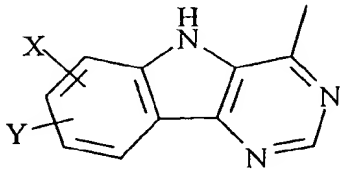
-$(CH_2)_n$-N-hexahydroazepine, -$(CH_2)_nNH_2$,-$(CH_2)_n$NH (C_1-C_6alkyl), -$(CH_2)_n$N(C_1-C_6alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E^1, E^2, E^3 or a monocyclic heteroaryl group, and each C_1-C_6 alkyl group can be substituted with -OH, -NH_2 or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

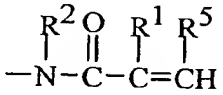
23. A compound of Claim 22 wherein Q is



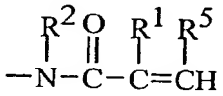
24. A compound of Claim 22 wherein Q is



25. A compound of Claim 23 wherein X is



26. A compound of Claim 24 wherein X is



27. A pharmaceutically acceptable composition that comprises a compound of Claim 1.

28. A pharmaceutically acceptable composition that comprises a compound of Claim 13.

29. A pharmaceutically acceptable composition that comprises a compound of Claim 22.

30. A method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Claim 1.

31. A method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis a therapeutically effective amount of a compound of Claim 1.

32. A method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Claim 13.

33. A method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis a therapeutically effective amount of a compound of Claim 13.

34. A method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Claim 22.

35. A method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis, a therapeutically effective amount of a compound of Claim 22.

36. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient a tyrosine kinase inhibition a tyrosine kinase inhibiting amount of a compound of Claim 1.

37. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient in need of tyrosine kinase inhibition a amount of tyrosine kinase inhibiting amount of a compound of Claim 13.

38. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient in need of tyrosine kinase inhibition a tyrosine kinase inhibiting amount of a compound of Claim 22.

39. A method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Claim 1.

40. A method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Claim 13.

41. A method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Claim 22.

42. A method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Claim 1.

43. A method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Claim 13.

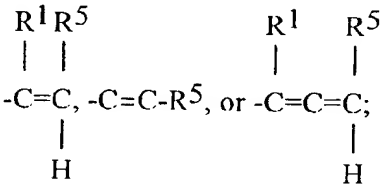
44. A method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Claim 22.

45. A method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Claim 1.

46. A method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Claim 13.

47. A method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Claim 22.

48. A compound according to Claim 1 wherein X is -D-E-F and F is



and R^5 is 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl,

$-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino,

-CH=CH-(C_1-C_6)alkyl, $-(CH_2)_n$-N-hexahydroazepine,

$-(CH_2)_nNH_2$, $-(CH_2)_nNH(C_1$-C_6 alkyl), $-(CH_2)_nN(C_1$-C_6 alkyl)$_2$,

-1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl,

N-(C_1-C_6)alkylcarbamoyl, and each C_1-C_1 alkyl group of

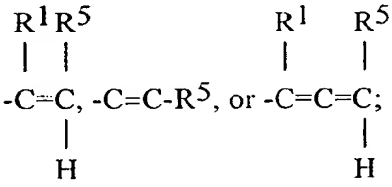
1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -CH=CH-(C_1-C_6)alkyl,

-1-oxo(C_1-C_6)alkyl, (C_1-C_6)alkyloxycarbonyl, or

-N-(C_1-C_6)alkylcarbamoyl is substituted with -OH, $-NH_2$, or

-NAB, where A and B are as defined above; or

Y is -D-E-F and F is



and R^5 is 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, $-(CH_2)_n$-N-piperidinyl,

$-(CH_2)_n$-piperazinyl, $-(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl],

$-(CH_2)_n$-N-pyrrolidyl, $-(CH2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl,

$-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino,

-CH=CH-(C_1-C_6)alkyl, $-(CH_2)_n$-N-hexahydroazepine,

$-(CH_2)_nNH_2$, $-(CH_2)_nNH(C_1$-C_6 alkyl), $-(CH_2)_nN(C_1$-C_6 alkyl)$_2$,

-1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl,

N-(C_1-C_6)alkylcarbamoyl, and each C_1-C_1 alkyl group of

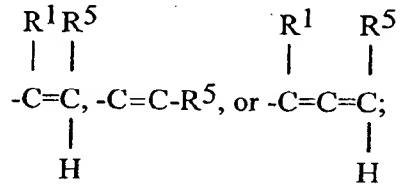
1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -CH–CH-(C_1-C_6)alkyl,

-1-oxo(C_1-C_6)alkyl, (C_1-C_6)alkyloxycarbonyl, or

-N-(C_1-C_6)alkylcarbamoyl is substituted with -OH, $-NH_2$, or

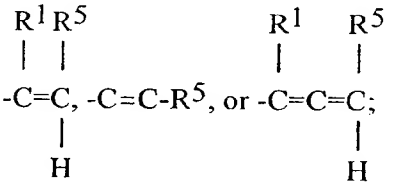
-NAB, where A and B are as defined above.

49. A compound according to Claim 13 wherein X is -D-E-F and F is



and R^5 is 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -(CH2)$_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -CH=CH-(C_1-C_6)alkyl, -$(CH_2)_n$-N-hexahydroazepine, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$NH($C_1$-$C_6$ alkyl), -$(CH_2)_n$N(C_1-C_6 alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, and each C_1-C_1 alkyl group of 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -CH=CH-(C_1-C_6)alkyl, -1-oxo(C_1-C_6)alkyl, (C_1-C_6)alkyloxycarbonyl, or -N-(C_1-C_6)alkylcarbamoyl is substituted with -OH, -NH_2, or -NAB, where A and B are as defined above; or

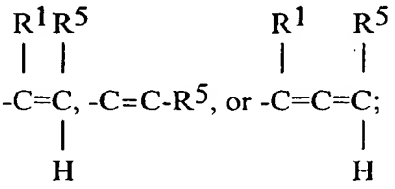
Y is -D-E-F and F is



and R^5 is 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -(CH2)$_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -CH=CH-(C_1-C_6)alkyl, -$(CH_2)_n$-N-hexahydroazepine, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$NH($C_1$-$C_6$ alkyl), -$(CH_2)_n$N(C_1-C_6 alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl,

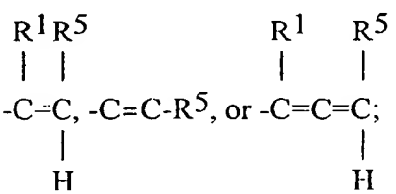
N-(C_1-C_6)alkylcarbamoyl, and each C_1-C_1 alkyl group of 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -CH=CH-(C_1-C_6)alkyl, -1-oxo(C_1-C_6)alkyl, (C_1-C_6)alkyloxycarbonyl, or -N-(C_1-C_6)alkylcarbamoyl is substituted with -OH, $-NH_2$, or -NAB, where A and B are as defined above.

50. A compound according to Claim 22 wherein X is -D-E-F and F is



and R^5 is 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -CH=CH-(C_1-C_6)alkyl, -$(CH_2)_n$-N-hexahydroazepine, -$(CH_2)_n$$NH_2$,-$(CH_2)_n$NH($C_1$-$C_6$ alkyl), -$(CH_2)_n$N(C_1-C_6 alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, and each C_1-C_1 alkyl group of 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -CH=CH-(C_1-C_6)alkyl, -1-oxo(C_1-C_6)alkyl, (C_1-C_6)alkyloxycarbonyl, or -N-(C_1-C_6)alkylcarbamoyl is substituted with -OH, $-NH_2$, or -NAB, where A and B are as defined above; or

Y is -D-E-F and F is



and R^5 is 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-piperazinyl, -$(CH_2)_n$-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -(CH2)$_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -CH=CH-(C_1-C_6)alkyl, -$(CH_2)_n$-N-hexahydroazepine, -$(CH_2)_nNH_2$,-$(CH_2)_nNH(C_1$-C_6 alkyl), -$(CH_2)_nN(C_1$-C_6 alkyl)$_2$, -1-oxo(C_1-C_6)alkyl, carboxy, (C_1-C_6)alkyloxycarbonyl, N-(C_1-C_6)alkylcarbamoyl, and each C_1-C_1 alkyl group of 1,1-difluoro(C_1-C_6)alkyl, C_1-C_6 alkyl, -CH=CH-(C_1-C_6)alkyl, -1-oxo(C_1-C_6)alkyl, (C_1-C_6)alkyloxycarbonyl, or -N-(C_1-C_6)alkylcarbamoyl is substituted with -OH, -NH_2, or -NAB, where A and B are as defined above.

51. A compound according to Claim 1 wherein X is -D-E-F;

Y is -SR^4, -OR^4, or -NHR^3;

and R^3 and R^4 are -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl;

or

Y is -D-E-F;

X is $-SR^4$, $-OR^4$, or $-NHR^3$;

and R^3 and R^4 are $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein the substituents are selected from -OH, $-NH_2$, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_nOH$, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl.

52. A compound according to Claim 13 wherein X is -D-E-F;

Y is $-SR^4$, $-OR^4$, or $-NHR^3$;

and R^3 and R^4 are $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein

A
|
the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl; or

Y is -D-E-F;

X is -SR^4, -OR^4, or -NHR^3;

and R^3 and R^4 are -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl, -$(CH_2)_n$-N-morpholino, -$(CH_2)_n$-N-thiomorpholino, -$(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein

A
|
the substituents are selected from -OH, -NH_2, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$OH, -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-N-pyridyl, -$(CH_2)_n$-imidazoyl, or -$(CH_2)_n$-N-imidazoyl.

53. A compound according to Claim 22 wherein X is -D-E-F;

Y is -SR^4, -OR^4, or -NHR^3;

and R^3 and R^4 are -$(CH_2)_n$-N-piperidinyl, -$(CH_2)_n$-N-piperazinyl, -$(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], -$(CH_2)_n$-N-pyrrolidyl, -$(CH_2)_n$-pyridinyl, -$(CH_2)_n$-N-imidazoyl, -$(CH_2)_n$-imidazoyl,

$-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino,

$-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein

the substituents are selected from -OH, $-NH_2$, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_nOH$, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl; or

Y is -D-E-F;

X is $-SR^4$, $-OR^4$, or $-NHR^3$;

and R^3 and R^4 are $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-pyridinyl, $-(CH_2)_n$-N-imidazoyl, $-(CH_2)_n$-imidazoyl, $-(CH_2)_n$-N-morpholino, $-(CH_2)_n$-N-thiomorpholino, $-(CH_2)_n$-N-hexahydroazepine or substituted C_1-C_6 alkyl, wherein

the substituents are selected from -OH, $-NH_2$, or -N-B, A and B are independently hydrogen, C_1-C_6 alkyl, $-(CH_2)_nOH$, $-(CH_2)_n$-N-piperidinyl, $-(CH_2)_n$-N-piperazinyl, $-(CH_2)_n$-N_1-piperazinyl[N_4-(C_1-C_6)alkyl], $-(CH_2)_n$-N-pyrrolidyl, $-(CH_2)_n$-N-pyridyl, $-(CH_2)_n$-imidazoyl, or $-(CH_2)_n$-N-imidazoyl.

54. The compounds:

N-[4-(6-Bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylamide;

N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]propynamide;

N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]propynamide;

N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]propynamide;

N-[4-(4-6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacryl-amide;

N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)quinazoline;

6-(S-Vinylsulfonamido)-4-(6-pyrrol-1-yl-2,3-dihydroindol-1-yl)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Pyrrol-1-yl-2,3-dihydroindol-1-yl)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylamide

N-[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(Octahydroindol-1-yl)-7-[3-(4-morpholino)propoxy]-quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Octahydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1{[4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(5-Methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(5-methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]amide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2,3,4,5-Tetrahydro-1H-benzoazepin-1-yl)pyrido[3,4-d]-pyrimid-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]-pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]-pyrimid-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]-pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]-pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)-pyrido[3,4-d]pyrimidine;

6-(S-Vinylsulfonamido)-4-(2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl) pyrido[3,4-d]pyrimidine;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(2,3,6,7,8,9-Hexahydro-1H-benzo[g]indol-1-yl)pyrido[3,4 d]-pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1{[4-(2,3-dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl) benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(2,3,5,6-Tetrahydropyrrolo[2,3-f]indol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)-7-[4-(N,N-dimethylamino)butoxy] quinazolin-6-yl]acrylate;

[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)-7-[3-(4-morpholino)-propoxy]quinazolin-6-yl] acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1{[4-(6-methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

[4-(6-Fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-7-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

N-[4-(Quinol-2-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Quinol-2-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(Indol-5-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(Quinol-3-ylamino)quinazolin-6-yl]propynamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]propynamide;

N-[4-(Quinol-3-ylamino)quinazolin-7-yl]propynamide;

N-[4-(Indol-5-ylamino)quinazolin-7-yl]propynamide;

N-[4-(Quinol-5-ylamino)quinazolin-6-yl]but-2-ynamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-ynamide;

N-[4-(Quinol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(Quinol-6-ylamino)quinazolin-6-yl]but-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-enamide;

N-[4-(Quinol-6-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(Quinol-7-ylamino)quinazolin-6-yl]-3-chloroacrylamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(quinol-7-ylamino)quinazoline;

6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(quinol-8-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]-quinazolin-6-yl]acrylamide;

N-[7-[4-(N,N-dimethylamino)butoxy]-4-(quinol-8-ylamino)-quinazolin-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylamide;

N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)-propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-6-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-6-ylamino) quinazolin-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino) quinazolin-6-yl]amide;

Pent-2-enedioic acid 1{[4-(indol-5-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(1H-indazol-6-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1H-Indazol-6-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(4-benzyloxyphenylamino)-quinazolin-6-yl]amide;

N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(1H-Indazol-4-ylamino)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid -6-yl]but-2-enamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(benzothiazol-5-ylamino)pyrido[3,4-d]-pyrimidine;

6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)pyrido[3,4-d]-pyrimidine;

N-[4-(Benzothiazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1{[4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1,2,3,4-Tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1,2,3,4-tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)-pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(benzo[c][2,1,3]thiadiazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)-pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(Benzo[c][2,1,3]thiadiazol-4-ylamino)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

[4-(Benzimidazol-5-ylamino)quinazolin-6-yl]acrylate;

[4-(Indol-5-ylamino)quinazolin-6-yl]acrylate;

[4-(Benzimidazol-5-ylamino)quinazolin-7-yl]acrylate;

[4-(Indol-5-ylamino)quinazolin-7-yl]acrylate;

[7-[3-(4-Morpholino)propoxy]-4-(benzimidazol-5-ylamino)-quinazolin-6-yl]acrylate;

[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]-quinazolin-6-yl]acrylate;

[7-[4-(N,N-dimethylamino)butoxy]-4-(6-methoxyquinol-8-ylamino)quinazolin-6-yl]acrylate;

[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-methoxyquinol-8-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(indol-5-ylamino)-quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1-methylindol-5-ylamino)quinazolin-6-yl]ester;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1{[4-(indol-5-ylamino)quinazolin-6-yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(1-methylindol-5-ylamino)quinazolin-6-yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(2-Methylindol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)-propylthio)but-2-enoate;

7-Morpholin-4-ylhept-2-ynoic acid [4-(3-cyanoindol-5-ylamino)-quinazolin-6-yl]ester;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)-quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(benzothien-5-ylamino)-quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]propynamide;

N-[4-(1-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-yl]propynamide;

N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]but-2-ynamide;

N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Benzylindol-6-ylamino)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(1-Benzylindol-6-ylamino)-7-[4-(N,N-dimethylamino)-butoxy]quinazolin-6-yl]acrylamide;

N-[4-(2-Phenylbenzimidazol-5-ylamino)-7-[3-(4-morpholino)-propoxy]quinazolin-6-yl]acrylamide;

N-[4-(2-Phenylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(42-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1-Benzylbenzotriazol-5-ylamino) quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(3-benzylbenzotriazol-5-ylamino) quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino) quinazolin-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(3-Benzylbenzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(1-phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimidine;

6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimidine;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzyloxybenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1{[4-(2-benzylsulfonylbenzimidazol-5-ylamino) pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(4-benzyloxybenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylsulfonylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

N-[4-(1-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1{[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate; and

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/15592

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/04 A61K31/505 C07D401/04 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 0 837 063 A (PFIZER) 22 April 1998 see claim 1	1-12
P,Y	WO 97 38983 A (WARNER LAMBERT CO ;BRIDGES ALEXANDER JAMES (US); DENNY WILLIAM ALE) 23 October 1997 see claim 1	1-12
Y	WO 97 22596 A (ZENECA LTD ;ZENECA PHARMA SA (FR); LOHMANN JEAN JACQUES MARCEL (FR) 26 June 1997 see claim 1	1-12
Y	WO 96 09294 A (WELLCOME FOUND ;HUDSON ALAN THOMAS (GB); VILE SADIE (GB); BARRACLO) 28 March 1996 see claim 1	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1998	15.01.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GETTINS M.P.

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/15592

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 475 001 A (BARKER ANDREW J) 12 December 1995 cited in the application see claim 1	1-12
Y	US 5 457 105 A (BARKER ANDREW J) 10 October 1995 cited in the application see claim 1	1-12
Y	WO 95 23141 A (PFIZER ;ARNOLD LEE D (US)) 31 August 1995 cited in the application see claim 1	1-12
Y	WO 95 19774 A (WARNER LAMBERT CO) 27 July 1995 cited in the application see claim 1	1-12
Y	EP 0 602 851 A (ZENECA LTD) 22 June 1994 see claim 1	1-12
Y	WO 95 15758 A (HSU CHIN YI JENNY ;ZILBERSTEIN ASHER (US); JOHNSON SUSAN E (US); M) 15 June 1995 Formula I see page 4	1-12

3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 15592

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 30 - 47
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 30-47 are directed to a method of treatment of the human/ animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13,27,30,31,36,39,42,45,48,51,54 (part)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13,27,30,31,36,39,42,45,48,51,54 (part)

   Compounds I

2. Claims: 13(part),14,21 (both complete),28,32,33,37,40,43, 46,49,52 (all partial)

   Compounds II where Q is as in claim 14.

3. Claims: 13(part),15,18 (both complete),28,32,33,37,40,43, 46,49,52 (all partial)

   Compounds II where Q is as in claim 15

4. Claims: 13(part),16,19,20 (all complete),28,32,33,37,40,43, 46,49,52,54 (all partial)

   Compounds II where Q is as in claim 16

5. Claims: 13(part),17 (complete),28,32,33,37,40,43,46,49,52, 54 (all partial)

   Compounds II where Q is as in claim 17

6. Claims: 22(part),23,25 (both complete), 29,34,35,38,41,44, 47,50,53, 54 (all part)

   Compounds III where Q is as in claim 23

7. Claims: 22(part),24,26 (both complete), 29,34,35,38,41,44, 47,50,53, 54 (all part)

   Compounds III where Q is as in claim 24

8. Claims: 22,29,34,35,38,41,44,47,50,53, 54 (all part)

   Compounds III where Q is the pyrimidoindole not covered by claim 24.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 22,29,34,35,38,41,44,47,50,53, 54 (all part)

Compounds III where Q is the quinazolinopyrrolo ring

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/15592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0837063 A	22-04-1998	CA 2218945 A	17-04-1998
		JP 10152477 A	09-06-1998
WO 9738983 A	23-10-1997	AU 2446397 A	07-11-1997
WO 9722596 A	26-06-1997	AU 1106197 A	14-07-1997
		CZ 9801882 A	16-09-1998
		EP 0873319 A	28-10-1998
		NO 982784 A	17-08-1998
WO 9609294 A	28-03-1996	AU 3482495 A	09-04-1996
		EP 0782570 A	09-07-1997
		JP 10505600 T	02-06-1998
US 5475001 A	12-12-1995	AU 7191694 A	20-02-1995
		EP 0635498 A	25-01-1995
		WO 9503283 A	02-02-1995
		JP 9500636 T	21-01-1997
		ZA 9405156 A	19-01-1995
US 5457105 A	10-10-1995	US 5616582 A	01-04-1997
		AT 130000 T	15-11-1995
		AU 661533 B	27-07-1995
		AU 3101093 A	22-07-1993
		CA 2086968 A,C	21-07-1993
		CZ 282038 B	16-04-1997
		DE 69300754 D	14-12-1995
		DE 69300754 T	28-03-1996
		DK 566226 T	18-03-1996
		EP 0566226 A	20-10-1993
		ES 2078798 T	16-12-1995
		FI 930208 A	21-07-1993
		GR 3018143 T	29-02-1996
		HK 36497 A	04-04-1997
		HU 9500185 A	28-07-1995
		MX 9300277 A	30-06-1994
		NO 301541 B	10-11-1997
		NZ 245662 A	26-09-1995
		SK 1693 A	09-09-1993
		ZA 9300015 A	20-07-1993
		JP 6073025 A	15-03-1994
WO 9523141 A	31-08-1995	AU 686843 B	12-02-1998
		AU 2972795 A	11-09-1995
		BR 9506936 A	09-09-1997
		CA 2183655 A	31-08-1995
		CN 1141633 A	29-01-1997
		CZ 9602413 A	16-07-1997
		EP 0746554 A	11-12-1996
		FI 963283 A	22-08-1996
		HU 76291 A	28-07-1997
		JP 9501953 T	25-02-1997
		NO 963506 A	22-10-1996
		NZ 278135 A	25-03-1998
		PL 315941 A	09-12-1996
		US 5736534 A	07-04-1998
WO 9519774 A	27-07-1995	US 5654307 A	05-08-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/15592

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9519774 A		AU	686334 B	05-02-1998
		AU	1731495 A	08-08-1995
		AU	686339 B	05-02-1998
		AU	1833495 A	08-08-1995
		BG	100614 A	31-03-1997
		BG	100615 A	28-02-1997
		CA	2177372 A	27-07-1995
		CA	2177392 A	27-07-1995
		CN	1139383 A	01-01-1997
		CN	1139430 A	01-01-1997
		CZ	9601970 A	17-09-1997
		CZ	9601971 A	16-07-1997
		EP	0742717 A	20-11-1996
		EP	0741711 A	13-11-1996
		FI	962855 A	13-09-1996
		FI	962856 A	25-09-1996
		HR	950033 A	31-10-1997
		HR	950034 A	31-10-1997
		HU	74590 A	28-01-1997
		HU	74589 A	28-01-1997
		JP	9508126 T	19-08-1997
		JP	9508127 T	19-08-1997
		MD	960211 A	30-04-1998
		MD	960217 A	30-04-1998
		NO	963093 A	24-07-1996
		NO	963094 A	24-07-1996
		PL	315632 A	25-11-1996
		PL	315633 A	25-11-1996
		SK	89496 A	08-10-1997
		SK	89596 A	06-08-1997
		WO	9519970 A	27-07-1997
		US	5679683 A	21-10-1997
		ZA	9500441 A	10-10-1995
		ZA	9500440 A	10-10-1995
EP 0602851 A	22-06-1994	AT	143956 T	15-10-1996
		AU	664496 B	16-11-1995
		AU	5072893 A	23-06-1994
		CA	2103383 A	11-06-1994
		CN	1094043 A	26-10-1994
		CZ	9302651 A	15-06-1994
		DE	69305310 D	14-11-1996
		DE	69305310 T	13-02-1997
		DK	602851 T	24-03-1997
		ES	2093367 T	16-12-1996
		FI	935431 A	11-06-1994
		GR	3021326 T	31-01-1997
		HU	65622 A	28-07-1994
		JP	6336481 A	06-12-1994
		MX	9307778 A	29-07-1994
		NO	934504 A	13-06-1994
		NZ	250218 A	25-06-1996
		US	5580870 A	03-12-1996
		ZA	9308594 A	10-06-1994
WO 9515758 A	15-06-1995	US	5480883 A	02-01-1996
		US	5710158 A	20-01-1998
		AU	1305095 A	27-06-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/15592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515758 A		EP 0871448 A	21-10-1998
		US 5795889 A	18-08-1998
		US 5646153 A	08-07-1997
		US 5721237 A	24-02-1998
		US 5714493 A	03-02-1998